CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

75-347

Generic Name: Omeprazole Delayed-release Capsules, 10 mg, 20 mg, and 40 mg

Sponsor: Andrx Pharmaceuticals, Inc.

Approval Date: November 16, 2001

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
75-347

CONTENTS

Reviews / Information Included in this ANDA Review.	
Approval Letter	X
Tentative Approval Letter	X
ANDAs	
Approvable Letter	
Final Printed Labeling	X
Medical Review(s)	
Chemistry Review(s)	X
EA/FONSI	
Pharmacology Review(s)	
Statistical Review(s)	
Microbiology Review(s)	
Clinical Pharmacology & Biopharmaceutics Reviews	
Bioequivalence Review(s)	X
Administrative Document(s)	X
Correspondence	X

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-347

APPROVAL LETTER

ANDA 75-347

NOV 16 2001

Andrx Pharmaceuticals, Inc.
Attention: Diane Servello
4955 Orange Drive
Fort Lauderdale, FL 33314

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated March 17, 1998, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Omeprazole Delayed-release Capsules, 10 mg, 20 mg and 40 mg.

Reference is also made to our tentative approval letter dated March 23, 2000, and to your amendments dated August 6, 1999, January 20, December 18, 2000, March 27, July 30, August 31, September 11, and November 9, 2001.

The listed drug product (RLD) referenced in your application, Prilosec Delayed-release Capsules of Astra Zeneca, L.P., is subject to periods of patent protection which expire on April 2, 2002 (U.S. Patent No. 4,508,905); January 30, 2006 (U.S. Patent No. 4,636,499); October 20, 2007 (U.S. Patent Nos. 4,853,230 and 4,786,505); August 2, 2010 (U.S. Patent No. 5,093,342); August 4, 2014 (U.S. Patent Nos. 5,599,794 and 5,629,305); April 9, 2019 (U.S. Patent Nos. 6,147,103, 6,191,148 and 6,166,213) May 10, 2019 (U.S. Patent No. 6,150,380). Your application originally contained Paragraph IV Certifications to the '342, '794, and '305 patents. These certifications were subsequently withdrawn pursuant to 21 CFR 314.94(a)(12)(iii) based upon your statement that they are "method of use" patents and that such uses are not included in your proposed labeling.

We note that although the '905 patent was issued on April 2, 1985, it was not listed with the Agency by the NDA holder until May 4, 2001. Your application was accepted for filing by the Office of Generic Drugs on March 17, 1998. Thus, pursuant to 21 CFR 314.94(a)(12)(vi), Andrx is not required to file an amended patent certification to address the '905 patent.

Your application also contains Paragraph IV Certifications to the '499, '230, '505, '103, '380, '213, and '148 patents under Section 505(j)(2)(A)(vii)(IV) of the Act.
Section 505(j)(5)(B)(iii) of the Act provides that approval shall be made effective immediately unless an action is brought for infringement of the patent which is the subject of the certification before the expiration of forty-five days from the date the notice provided under paragraph (2)(B)(i) is received. You have notified FDA that Andrx Pharmaceuticals, Inc. (Andrx) has complied with the requirements of Section 505(j)(2)(B) of the Act and no action for patent infringement regarding the '103, '380, '213 and '148 patents was brought against Andrx within the statutory forty-five day period. You further informed the Agency that litigation is underway in the United States District Court for the Southern District of Florida involving a challenge to the '499, '505 and '230 patents (Astra Aktiebolag, Aktiebolaget Hassle, Astra Merck Enterprises Inc. and Astra Merck Inc. v. Andrx Pharmaceuticals, Inc., Civil Action No. 98-6521). With respect to this litigation, the Agency recognizes that the 30-month period identified in Section 505(j)(5)(B)(iii) of the Act, during which time FDA was precluded from approving your application, has expired.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Omeprazole Delayed-release Capsules, 10 mg, 20 mg, and 40 mg to be bioequivalent and, therefore, therapeutically equivalent to the listed drug, Prilosec® Delayed-release Capsules, 10 mg, 20 mg, and 40 mg, respectively.

Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application. The "interim" dissolution specifications are as follows:

> Dissolution testing should be conducted in
>
> 900 mL of 0.1N HCl for 2 hours [Acid stage]; followed by 900 mL of 0.05M phosphate buffer, pH 6.8 [buffer stage] at 37° C using USP 24 Apparatus I (basket) at 100 rpm. The test product should meet the following specifications:
>
> > NMT — of the drug in the capsule is dissolved in 2 hours [acid stage]; and

NLT __ of the drug in the capsule is dissolved in 45 minutes [buffer stage]

These "interim" dissolution test(s) and tolerances should be finalized by submitting dissolution data for the first three production size batches. Data should be submitted as a Special Supplement - Changes Being Effected when there are no revisions to the "interim" specifications or when the final specifications are tighter than the "interim" specifications. In all other instances, the information should be submitted in the form of a Prior Approval Supplement.

The issue of 180-day generic drug exclusivity is addressed in a separate letter dated November 16, 2001.

If you have any questions concerning the effective date of approval of an abbreviated new drug application and the Agency's elimination of the requirement that an ANDA applicant successfully defend a patent infringement suit to be eligible for 180-days of marketing exclusivity, please refer to the interim rule published in the November 5, 1998 Federal Register (Volume 63, No. 214, 59710).

Under Section 506A of the Act, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing,

Advertising, and Communications (HFD-40) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

/S/

Gary Buehler 11/16/01
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-347

TENTATIVE APPROVAL LETTER

ANDA 75-347 March 24, 2000

Andrx Pharmaceuticals, Inc.
Attention: Diane Servello
4001 S.W. 47th Avenue
Fort Lauderdale, FL 33314

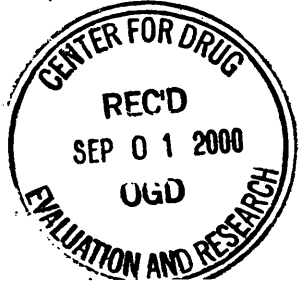
Dear Sir:

This is in reference to your abbreviated new drug application dated March 17, 1998, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Omeprazole Delayed-release Capsules, 10 mg, 20 mg and 40 mg.

Reference is also made to your amendments dated April 17 and August 14, 1998; March 26, April 9, June 14, July 28 and August 6, 1999; and January 20, 2000.

We have completed the review of this abbreviated application and have concluded that, based upon the information you have presented to date, the drug is safe and effective for use as recommended in the submitted labeling. Therefore, the application is **tentatively approved**. This determination is based upon information available to the Agency at this time (i.e., information in your application and the status of current good manufacturing practices of the facilities used in the manufacturing and testing of the drug product) and is therefore subject to change on the basis of new information that may come to our attention. This letter does not address notice issues related to the 180-day exclusivity provisions under section 505(j)(5)(B)(iv) of the Act.

The listed drug product referenced in your application is subject to a period of patent protection which expires on April 15, 2001, (Patent No.4,255,431), May 30, 2005, (Patent No.4,636,499), April 20, 2007, (Patent Nos. 4,853,230 and 4,786,505), February 2, 2010, (Patent No. 5,093,342) and February 4, 2014, (Patent Nos. 5,599,794 and 5,629,305). However, litigation is underway in the United States District Court for the Southern District of Florida involving a challenge to the patent (Astra Aktiebolag, Aktiebolaget Hassle, Astra Merck Enterprises Inc. and Astra Merck Inc. v. Andrx Pharmaceuticals, Inc., Civil Action No. 98-6521).



Therefore, final approval cannot be granted until:

1. a. the expiration of the 30-month period provided for in section 505(j)(5)(B)(iii) since the date of receipt of the 45-day notice required under section 505(j)(2)(B)(i), unless the court has extended or reduced the period because of the failure of either party to reasonably cooperate in expediting the action, or,

   b. the date of court decision [505(j)(5)(B)(iii)(I), (II), or (III)], which has been interpreted by the Agency to mean the date of the final order or judgement of that court from which no appeal can be or has been taken, or,

   c. the patent has expired, and

2. The Agency is assured there is no new information that would affect whether final approval should be granted.

Because the Agency is granting a tentative approval for this application, when you believe that your application may be considered for final approval, you must amend your application to notify the Agency whether circumstances have or have not arisen that may affect the effective date of final approval. Your amendment must provide:

1. a copy of a final order or judgement from which no appeal may be taken (which might not be the one from the district court), or a settlement agreement between the parties, whichever is applicable, or a licensing agreement between you and the patent holder, or any other relevant information, and

2. a. updated information related to labeling or chemistry, manufacturing and controls data, or any other change in the conditions outlined in this abbreviated application, or

   b. a statement that no such changes have been made to the application since the date of tentative approval.

Any changes in the conditions outlined in this abbreviated application and the status of the manufacturing and testing facilities' compliance with current good manufacturing

procedures are subject to Agency review before final approval of the
application will be made.

In addition to, or instead of, the amendments referred to above, the Agency may, at any time prior to the final date of approval, request that you submit amendments containing the information requested above.

Failure to submit either or both amendments may result in rescission of this tentative approval determination, or delay in issuance of the final approval letter.

The drug product that is the subject of this abbreviated application may not be marketed without final Agency approval under section 505 of the Act. The introduction or delivery for introduction into interstate commerce of this drug before the effective final approval date is prohibited under section 501 of the Act. Also, until the Agency issues the final approval letter, this drug product will not be listed in the Agency's "Approved Drug Products with Therapeutic Equivalence Evaluations" list.

The amendment should be designated as a MINOR AMENDMENT in your cover letter. Before you submit the amendment, please contact Kassandra Sherrod, Project Manager, at (301) 827•5849, for further instructions.

Sincerely yours,

Janet Woodcock
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-347

Final Printed Labeling

OMEPRAZOLE DELAYED-RELEASE CAPSULES

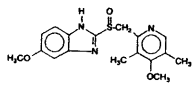
℞ Only

NOV 10

APPROVED

DESCRIPTION

The active ingredient in Omeprazole Delayed-release Capsules is a substituted benzimidazole, 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl) methyl] sulfinyl]-1*H*-benzimidazole, a compound that inhibits gastric acid secretion. Its empirical formula is $C_{17}H_{19}N_3O_3S$, with a molecular weight of 345.42. The structural formula is:



Omeprazole is a white to off-white crystalline powder which melts with decomposition at about 155°C. It is a weak base, freely soluble in ethanol and methanol, and slightly soluble in acetone and isopropanol and very slightly soluble in water. The stability of omeprazole is a function of pH; it is rapidly degraded in acid media, but has acceptable stability under alkaline conditions.

Omeprazole delayed-release capsules are supplied as delayed-release capsules for oral administration. Each delayed-release capsule contains either 10 mg, 20 mg or 40 mg of omeprazole in the form of enteric-coated pellets with the following inactive ingredients: cetyl alcohol, disodium phosphate, hydroxypropyl methylcellulose phthalate, lactose monohydrate, povidone, sodium lauryl sulfate, sucrose and talc. The capsule shells and imprinting inks have the following inactive ingredients: ammonium hydroxide, D&C Yellow #10, ethyl alcohol, FD&C Blue #2 Aluminum Lake, FD&C Green #3, gelatin-NF, propylene glycol, shellac, and titanium dioxide.

CLINICAL PHARMACOLOGY

Pharmacokinetics and Metabolism: Omeprazole

Omeprazole delayed-release capsules contain an enteric-coated pellet formulation of omeprazole (because omeprazole is acid-labile), so that absorption of omeprazole begins only after the pellets leave the stomach. Absorption is rapid, with peak plasma levels of omeprazole occurring within 0.5 to 3.5 hours. Peak plasma concentrations of omeprazole and AUC are approximately proportional to doses up to 40 mg, but because of a saturable first-pass effect, a greater than linear response in peak plasma concentration and AUC occurs with doses greater than 40 mg. Absolute bioavailability (compared to intravenous administration) is about 30 to 40% at doses of 20 to 40 mg, due in large part to presystemic metabolism. In healthy subjects the plasma half-life is 0.5 to 1 hour, and the total body clearance is 500 to 600 mL/min. Protein binding is approximately 95%.

The bioavailability of omeprazole increases slightly upon repeated administration of omeprazole delayed-release capsules.

Following single dose oral administration of a buffered solution of omeprazole, little if any unchanged drug was excreted in urine. The majority of the dose (about 77%) was eliminated in urine as at least six metabolites. Two were identified as hydroxyomeprazole and the corresponding carboxylic acid. The remainder of the dose was recoverable in feces. This implies a significant biliary excretion of the metabolites of omeprazole. Three metabolites have been identified in plasma - the sulfide and sulfone derivatives of omeprazole, and hydroxyomeprazole. These metabolites have very little or no antisecretory activity.

In patients with chronic hepatic disease, the bioavailability increased to approximately 100% compared to an I.V. dose, reflecting decreased first-pass effect, and the plasma half-life of the drug increased to nearly 3 hours compared to the half-life in normals of 0.5 to 1 hour. Plasma clearance averaged 70 mL/min, compared to a value of 500 to 600 mL/min in normal subjects.

In patients with chronic renal impairment, whose creatinine clearance ranged between 10 and 62 mL/min/1.73 m^2, the disposition of omeprazole was very similar to that in healthy volunteers, although there was a slight increase in bioavailability. Because urinary excretion is a primary route of excretion of omeprazole metabolites, their elimination slowed in proportion to the decreased creatinine clearance.

The elimination rate of omeprazole was somewhat decreased in the elderly, and bioavail-

have been identified in plasma - the sulfide and sulfone derivatives of omeprazole, and hydroxyomeprazole. These metabolites have very little or no antisecretory activity.

In patients with chronic hepatic disease, the bioavailability increased to approximately 100% compared to an I.V. dose, reflecting decreased first-pass effect, and the plasma half-life of the drug increased to nearly 3 hours compared to the half-life in normals of 0.5 to 1 hour. Plasma clearance averaged 70 mL/min, compared to a value of 500 to 600 mL/min in normal subjects.

In patients with chronic renal impairment, whose creatinine clearance ranged between 10 and 62 mL/min/1.73 m^2, the disposition of omeprazole was very similar to that in healthy volunteers, although there was a slight increase in bioavailability. Because urinary excretion is a primary route of excretion of omeprazole metabolites, their elimination slowed in proportion to the decreased creatinine clearance.

The elimination rate of omeprazole was somewhat decreased in the elderly, and bioavailability was increased. Omeprazole was 76% bioavailable when a single 40 mg oral dose of omeprazole (buffered solution) was administered to healthy elderly volunteers, versus 58% in young volunteers given the same dose. Nearly 70% of the dose was recovered in urine as metabolites of omeprazole and no unchanged drug was detected. The plasma clearance of omeprazole was 250 mL/min (about half that of young volunteers) and its plasma half-life averaged one hour, about twice that of young healthy volunteers.

In pharmacokinetic studies of single 20 mg omeprazole doses, an increase in AUC of approximately four-fold was noted in Asian subjects compared to Caucasians.

Dose adjustment, particularly where maintenance of healing of erosive esophagitis is indicated, for the hepatically impaired and Asian subjects should be considered.

Omeprazole delayed-release capsule 40 mg was bioequivalent when administered with and without applesauce. However, omeprazole delayed-release 20 mg was not bioequivalent when administered with and without applesauce. When administered with applesauce, a mean 25% reduction in C_{max} was observed without a significant change AUC for omeprazole delayed-release capsules 20 mg. The clinical relevance of this finding is unknown.

Pharmacodynamics

Mechanism of Action

Omeprazole belongs to a new class of antisecretory compounds, the substituted benzimidazoles, that do not exhibit anticholinergic or H_2 histamine antagonistic properties, but that suppress gastric acid secretion by specific inhibition of the H^+/K^+ ATPase enzyme system at the secretory surface of the gastric parietal cell. Because this enzyme system is regarded as the acid (proton) pump within the gastric mucosa, omeprazole has been characterized as a gastric acid-pump inhibitor, in that it blocks the final step of acid production. This effect is dose-related and leads to inhibition of both basal and stimulated acid secretion irrespective of the stimulus. Animal studies indicate that after rapid disappearance from plasma, omeprazole can be found within the gastric mucosa for a day or more.

Antisecretory Activity

After oral administration, the onset of the antisecretory effect of omeprazole occurs within one hour, with the maximum effect occurring within two hours. Inhibition of secretion is about 50% of maximum at 24 hours and the duration of inhibition lasts up to 72 hours. The antisecretory effect thus lasts far longer than would be expected from the very short (less than one hour) plasma half-life, apparently due to prolonged binding to the parietal H^+/K^+ ATPase enzyme. When the drug is discontinued, secretory activity returns gradually, over 3 to 5 days. The inhibitory effect of omeprazole on acid secretion increases with repeated once-daily dosing, reaching a plateau after four days.

Results from numerous studies of the antisecretory effect of multiple doses of 20 mg and 40 mg of omeprazole in normal volunteers and patients are shown below. The "max" value represents determinations at a time of maximum effect (2 to 6 hours after dosing), while "min" values are those 24 hours after the last dose of omeprazole.

Range of Mean Values from Multiple Studies of the Mean Antisecretory Effects of Omeprazole After Multiple Daily Dosing

Parameter	Omeprazole 20 mg		Omeprazole* 40 mg	
	Max	Min	Max	Min
% Decrease in Basal Acid Output	78*	58 to 80	94*	80 to 93
% Decrease om Peak Acid Output	79*	50 to 59	88*	62 to 68
% Decrease in 24-hr. Intragastric Acidity		80 to 97		92 to 94

*Single Studies

Single daily oral doses of omeprazole ranging from a dose of 10 mg to 40 mg have produced 100% inhibition of 24-hour intragastric acidity in some patients.

Enterochromaffin-like (ECL) Cell Effects

In 24-month carcinogenicity studies in rats, a dose-related significant increase in gastric carcinoid tumors and ECL cell hyperplasia was observed in both male and female animals (see PRECAUTIONS, *Carcinogenesis, Mutagenesis, Impairment of Fertility*). Carcinoid tumors have also been observed in rats subjected to fundectomy or long-term treatment with other proton pump inhibitors or high doses of H_2-receptor antagonists.

Human gastric biopsy specimens have been obtained from more than 3000 patients treated with omeprazole in long-term clinical trials. The incidence of ECL cell hyperplasia in these studies increased with time; however, no case of ECL cell carcinoids, dysplasia, or neoplasia has been found in these patients. (See also CLINICAL PHARMACOLOGY, *Pathological Hypersecretory Conditions*.)

Serum Gastrin Effects

In studies involving more than 200 patients, serum gastrin levels increased during the first 1 to 2 weeks of once-daily administration of therapeutic doses of omeprazole in parallel with inhibition of acid secretion. No further increase in serum gastrin occurred with continued treatment. In comparison with histamine H_2-receptor antagonists, the median increases produced by 20 mg doses of omeprazole were higher (1.3 to 3.6 fold vs. 1.1 to 1.8 fold increase). Gastrin values returned to pretreatment levels, usually within 1 to 2 weeks after discontinuation of therapy.

Other Effects

Systemic effects of omeprazole in the CNS, cardiovascular and respiratory systems have not been found to date. Omeprazole, given in oral doses of 30 or 40 mg for 2 to 4 weeks, had no effect on thyroid function, carbohydrate metabolism, or circulating levels of

was observed in both male and female animals (see PRECAUTIONS, *Carcinogenesis, Mutagenesis, Impairment of Fertility*). Carcinoid tumors have also been observed in rats subjected to fundectomy or long-term treatment with other proton pump inhibitors or high doses of H_2-receptor antagonists.
Human gastric biopsy specimens have been obtained from more than 3000 patients treated with omeprazole in long-term clinical trials. The incidence of ECL cell hyperplasia in these studies increased with time; however, no case of ECL cell carcinoids, dysplasia, or neoplasia has been found in these patients. (See also CLINICAL PHARMACOLOGY, *Pathological Hypersecretory Conditions*.)

Serum Gastrin Effects
In studies involving more than 200 patients, serum gastrin levels increased during the first 1 to 2 weeks of once-daily administration of therapeutic doses of omeprazole in parallel with inhibition of acid secretion. No further increase in serum gastrin occurred with continued treatment. In comparison with histamine H_2-receptor antagonists, the median increases produced by 20 mg doses of omeprazole were higher (1.3 to 3.6 fold vs. 1.1 to 1.8 fold increase). Gastrin values returned to pretreatment levels, usually within 1 to 2 weeks after discontinuation of therapy.

Other Effects
Systemic effects of omeprazole in the CNS, cardiovascular and respiratory systems have not been found to date. Omeprazole, given in oral doses of 30 or 40 mg for 2 to 4 weeks, had no effect on thyroid function, carbohydrate metabolism, or circulating levels of parathyroid hormone, cortisol, estradiol, testosterone, prolactin, cholecystokinin or secretin.
No effect on gastric emptying of the solid and liquid components of a test meal was demonstrated after a single dose of omeprazole 90 mg. In healthy subjects, a single I.V. dose of omeprazole (0.35 mg/kg) had no effect on intrinsic factor secretion. No systematic dose-dependent effect has been observed on basal or stimulated pepsin output in humans. However, when intragastric pH is maintained at 4.0 or above, basal pepsin output is low, and pepsin activity is decreased.
As do other agents that elevate intragastric pH, omeprazole administered for 14 days in healthy subjects produced a significant increase in the intragastric concentrations of viable bacteria. The pattern of the bacterial species was unchanged from that commonly found in saliva. All changes resolved within three days of stopping treatment.

Clinical Studies
Duodenal Ulcer Disease
Active Duodenal Ulcer: In a multicenter, double-blind, placebo-controlled study of 147 patients with endoscopically documented duodenal ulcer, the percentage of patients healed (per protocol) at 2 and 4 weeks was significantly higher with omeprazole delayed-release capsules 20 mg once a day than with placebo ($p \leq 0.01$).

Treatment of Active Duodenal Ulcer
% of Patients Healed

	Omeprazole Delayed-release Capsules 20 mg a.m. (n=99)	Placebo a.m. (n=48)
Week 2	*41	13
Week 4	*75	27

*($p \leq 0.01$)

Complete daytime and nighttime pain relief occurred significantly faster ($p \leq 0.01$) in patients treated with omeprazole delayed-release capsules 20 mg than in patients treated with placebo. At the end of the study, significantly more patients who had received omeprazole delayed-release capsules had complete relief of daytime pain ($p \leq 0.05$) and nighttime pain ($p \leq 0.01$).
In a multicenter, double-blind study of 293 patients with endoscopically documented duodenal ulcer, the percentage of patients healed (per protocol) at 4 weeks was significantly higher with omeprazole delayed-release capsules 20 mg once a day than with ranitidine 150 mg b.i.d. ($p<0.01$).

Treatment of Active Duodenal Ulcer
% of Patients Healed

	Omeprazole Delayed-release Capsules 20 mg a.m. (n=145)	Ranitidine 150 mg b.i.d. (n=148)
Week 2	42	34
Week 4	*82	63

*($p<0.01$)

Healing occurred significantly faster in patients treated with omeprazole delayed-release capsules than in those treated with ranitidine 150 mg b.i.d. ($p<0.01$).
In a foreign multinational randomized, double-blind study of 105 patients with endoscopically documented duodenal ulcer, 20 mg and 40 mg of omeprazole delayed-release capsules were compared to 150 mg b.i.d. of ranitidine at 2, 4 and 8 weeks. At 2 and 4 weeks both doses of omeprazole delayed-release capsules were statistically superior (per protocol) to ranitidine, but 40 mg was not superior to 20 mg of omeprazole delayed-release capsules, and at 8 weeks there was no significant difference between any of the active drugs.

Treatment of Active Duodenal Ulcer
% of Patients Healed

	Omeprazole Delayed-release Capsules		Ranitidine
	20 mg (n=34)	40 mg (n=36)	150 mg b.i.d. (n=35)
Week 2	*83	*83	53
Week 4	*97	*100	82
Week 8	100	100	94

*($p \leq 0.01$)

Gastric Ulcer
In a U.S. multicenter, double-blind, study of omeprazole 40 mg once a day, 20 mg once a day, and placebo in 520 patients with endoscopically diagnosed gastric ulcer, the following results were obtained.

Treatment of Gastric Ulcer
% of Patients Healed
(All Patients Treated)

	Omeprazole Delayed-release Capsules 20 mg q.d. (n=202)	Omeprazole Delayed-release Capsules 40 mg q.d. (n=214)	Placebo (n=104)
Week 4	47.5**	55.6**	30.8
Week 8	74.8**	82.7**+	48.1

**($p<0.01$) Omeprazole delayed-release capsules 40 mg or 20 mg versus placebo
+($p<0.05$) Omeprazole delayed-release capsules 40 mg versus 20 mg

For the stratified groups of patients with ulcer size less than or equal to 1 cm, no difference in healing rates between 40 mg and 20 mg was detected at either 4 or 8 weeks. For patients with ulcer size greater than 1 cm, 40 mg was significantly more effective than 20 mg at 8 weeks.
In a foreign, multinational, double-blind study of 602 patients with endoscopically diagnosed

% of Patients Healed			
	Omeprazole Delayed-release Capsules		Ranitidine
	20 mg (n=34)	40 mg (n=36)	150 mg b.i.d. (n=35)
Week 2	*83	*83	53
Week 4	*97	*100	82
Week 8	100	100	94

*($p \leq 0.01$)

Gastric Ulcer

In a U.S. multicenter, double-blind, study of omeprazole 40 mg once a day, 20 mg once a day, and placebo in 520 patients with endoscopically diagnosed gastric ulcer, the following results were obtained.

Treatment of Gastric Ulcer
% of Patients Healed
(All Patients Treated)

	Omeprazole Delayed-release Capsules 20 mg q.d. (n=202)	Omeprazole Delayed-release Capsules 40 mg q.d. (n=214)	Placebo (n=104)
Week 4	47.5**	55.6**	30.8
Week 8	74.8**	82.7**,†	48.1

**($p<0.01$) Omeprazole delayed-release capsules 40 mg or 20 mg versus placebo
*($p<0.05$) Omeprazole delayed-release capsules 40 mg versus 20 mg

For the stratified groups of patients with ulcer size less than or equal to 1 cm, no difference in healing rates between 40 mg and 20 mg was detected at either 4 or 8 weeks. For patients with ulcer size greater than 1 cm, 40 mg was significantly more effective than 20 mg at 8 weeks.

In a foreign, multinational, double-blind study of 602 patients with endoscopically diagnosed gastric ulcer, omeprazole 40 mg once a day, 20 mg once a day, and ranitidine 150 mg twice a day were evaluated.

Treatment of Gastric Ulcer
% of Patients Healed
(All Patients Treated)

	Omeprazole Delayed-release Capsules 20 mg q.d. (n=200)	Omeprazole Delayed-release Capsules 40 mg q.d. (n=187)	Ranitidine 150 mg b.i.d. (n=199)
Week 4	63.5	78.1**,††	56.3
Week 8	81.5	91.4**,††	78.4

**($p<0.01$) Omeprazole delayed-release capsules 40 mg versus ranitidine
††($p<0.01$) Omeprazole delayed-release capsules 40 mg versus 20 mg

Gastroesophageal Reflux Disease (GERD)

Symptomatic GERD: A placebo controlled study was conducted in Scandinavia to compare the efficacy of omeprazole 20 mg or 10 mg once daily for up to 4 weeks in the treatment of heartburn and other symptoms in GERD patients without erosive esophagitis. Results are shown below.

% Successful Symptomatic Outcome[a]			
	Omeprazole Delayed-release Capsules 20 mg a.m.	Omeprazole Delayed-release Capsules 10 mg a.m.	Placebo a.m.
All patients	46*,† (n=205)	31† (n=199)	13 (n=105)
Patients with confirmed GERD	56*,† (n=115)	36† (n=109)	14 (n=59)

[a]Defined as complete resolution of heartburn
*($p<0.005$) versus 10 mg
†($p<0.005$) versus placebo

Erosive Esophagitis: In a U.S. multicenter double-blind placebo controlled study of 20 mg or 40 mg of omeprazole delayed-release capsules in patients with symptoms of GERD and endoscopically diagnosed erosive esophagitis of grade 2 or above, the percentage healing rates (per protocol) were as follows:

Week	20 mg Omeprazole Delayed-release Capsules (n=83)	40 mg Omeprazole Delayed-release Capsules (n=87)	Placebo (n=43)
4	39**	45**	7
8	74**	75**	14

**($p<0.01$) Omeprazole delayed-release capsules versus placebo.

In this study, the 40 mg dose was not superior to the 20 mg dose of omeprazole delayed-release capsules in the percentage healing rate. Other controlled clinical trials have also shown that omeprazole delayed-release capsules is effective in severe GERD. In comparisons with histamine H_2-receptor antagonists in patients with erosive esophagitis, grade 2 or above, omeprazole delayed-release capsules in a dose of 20 mg was significantly more effective than the active controls. Complete daytime and nighttime heartburn relief occurred significantly faster ($p<0.01$) in patients treated with omeprazole delayed-release capsules than in those taking placebo or histamine H_2-receptor antagonists.

In this and five other controlled GERD studies, significantly more patients taking 20 mg omeprazole (84%) reported complete relief of GERD symptoms than patients receiving placebo (12%).

Long Term Maintenance Treatment of Erosive Esophagitis: In a U.S. double-blind, randomized, multicenter, placebo controlled study, two dose regimens of omeprazole delayed-release capsules were studied in patients with endoscopically confirmed healed esophagitis. Results to determine maintenance of healing of erosive esophagitis are shown below.

Life Table Analysis

	Omeprazole Delayed-release Capsules 20 mg q.d. (n=138)	Omeprazole Delayed-release Capsules 20 mg 3 days per week (n=137)	Placebo (n=131)
Percent in endoscopic remission at 6 months	*70	34	11

*($p<0.01$) Omeprazole delayed-release capsules 20 mg q.d. versus omeprazole delayed-release capsules 20 mg 3 consecutive days per week or placebo.

In an international multicenter double-blind study, omeprazole delayed-release capsules 20 mg daily and 10 mg daily were compared to ranitidine 150 mg twice daily in patients with endoscopically confirmed healed esophagitis. The table below provides the results of this study for maintenance of healing of erosive esophagitis.

Life Table Analysis

	Omeprazole Delayed-release Capsules 20 mg q.d. (n=131)	Omeprazole Delayed-release Capsules 10 mg q.d. (n=133)	Ranitidine 150 mg b.i.d. (n=128)
Percent in endoscopic remission at			

Week	20 mg Omeprazole Delayed-release Capsules (n=83)	40 mg Omeprazole Delayed-release Capsules (n=87)	Placebo (n=43)
4	39**	45**	7
8	74**	75**	14

**(p<0.01) Omeprazole delayed-release capsules versus placebo.

In this study, the 40 mg dose was not superior to the 20 mg dose of omeprazole delayed-release capsules in the percentage healing rate. Other controlled clinical trials have also shown that omeprazole delayed-release capsules is effective in severe GERD. In comparisons with histamine H_2-receptor antagonists in patients with erosive esophagitis, grade 2 or above, omeprazole delayed-release capsules in a dose of 20 mg was significantly more effective than the active controls. Complete daytime and nighttime heartburn relief occurred significantly faster (p<0.01) in patients treated with omeprazole delayed-release capsules than in those taking placebo or histamine H_2-receptor antagonists.
In this and five other controlled GERD studies, significantly more patients taking 20 mg omeprazole (84%) reported complete relief of GERD symptoms than patients receiving placebo (12%).

Long Term Maintenance Treatment of Erosive Esophagitis: In a U.S. double-blind, randomized, multicenter, placebo controlled study, two dose* regimens of omeprazole delayed-release capsules were studied in patients with endoscopically confirmed healed esophagitis. Results to determine maintenance of healing of erosive esophagitis are shown below.

Life Table Analysis

	Omeprazole Delayed-release Capsules 20 mg q.d. (n=138)	Omeprazole Delayed-release Capsules 20 mg 3 days per week (n=137)	Placebo (n=131)
Percent in endoscopic remission at 6 months	*70	34	11

*(p<0.01) Omeprazole delayed-release capsules 20 mg q.d. versus omeprazole delayed-release capsules 20 mg 3 consecutive days per week or placebo.

In an international multicenter double-blind study, omeprazole delayed-release capsules 20 mg daily and 10 mg daily were compared to ranitidine 150 mg twice daily in patients with endoscopically confirmed healed esophagitis. The table below provides the results of this study for maintenance of healing of erosive esophagitis.

Life Table Analysis

	Omeprazole Delayed-release Capsules 20 mg q.d. (n=131)	Omeprazole Delayed-release Capsules 10 mg q.d. (n=133)	Ranitidine 150 mg b.i.d. (n=128)
Percent in endoscopic remission at 12 months	*77	‡58	46

*(p=0.01) Omeprazole delayed-release capsules 20 mg q.d. versus omeprazole delayed-release capsules 10 mg q.d. or ranitidine.
‡(p=0.03) Omeprazole delayed-release capsules 10 mg q.d. versus ranitidine.

In patients who initially had grades 3 or 4 erosive esophagitis, for maintenance after healing 20 mg daily of omeprazole delayed-release capsules was effective, while 10 mg did not demonstrate effectiveness.

Pathological Hypersecretory Conditions
In open studies of 136 patients with pathological hypersecretory conditions, such as Zollinger-Ellison (ZE) syndrome with or without multiple endocrine adenomas, omeprazole delayed-release capsules significantly inhibited gastric acid secretion and controlled associated symptoms of diarrhea, anorexia, and pain. Doses ranging from 20 mg every other day to 360 mg per day maintained basal acid secretion below 10 mEq/hr in patients without prior gastric surgery, and below 5 mEq/hr in patients with prior gastric surgery.
Initial doses were titrated to the individual patient need, and adjustments were necessary with time in some patients (see DOSAGE AND ADMINISTRATION). Omeprazole delayed-release capsules was well tolerated at these high dose levels for prolonged periods (>5 years in some patients). In most ZE patients, serum gastrin levels were not modified by omeprazole delayed-release capsules. However, in some patients serum gastrin increased to levels greater than those present prior to initiation of omeprazole therapy. At least 11 patients with ZE syndrome on long-term treatment with omeprazole delayed-release capsules developed gastric carcinoids. These findings are believed to be a manifestation of the underlying condition, which is known to be associated with such tumors, rather than the result of the administration of omeprazole delayed-release capsules. (See ADVERSE REACTIONS.)

INDICATIONS AND USAGE

Duodenal Ulcer
Omeprazole delayed-release capsules are indicated for short-term treatment of active duodenal ulcer. Most patients heal within four weeks. Some patients may require an additional four weeks of therapy.

Gastric Ulcer
Omeprazole delayed-release capsules are indicated for short-term treatment (4 to 8 weeks) of active benign gastric ulcer. (See CLINICAL PHARMACOLOGY, *Clinical Studies, Gastric Ulcer.*)

Treatment of Gastroesophageal Reflux Disease (GERD)
Symptomatic GERD
Omeprazole delayed-release capsules are indicated for the treatment of heartburn and other symptoms associated with GERD.

Erosive Esophagitis
Omeprazole delayed-release capsules are indicated for the short-term treatment (4 to 8 weeks) of erosive esophagitis which has been diagnosed by endoscopy.
(See CLINICAL PHARMACOLOGY, *Clinical Studies.*)
The efficacy of omeprazole delayed-release capsules used for longer than 8 weeks in these patients has not been established. In the rare instance of a patient not responding to 8 weeks of treatment, it may be helpful to give up to an additional 4 weeks of treatment. If there is recurrence of erosive esophagitis or GERD symptoms (e.g. heartburn), additional 4 to 8 week courses of omeprazole may be considered.

Maintenance of Healing of Erosive Esophagitis
Omeprazole delayed-release capsules are indicated to maintain healing of erosive esophagitis.
Controlled studies do not extend beyond 12 months.

Pathological Hypersecretory Conditions
Omeprazole delayed-release capsules are indicated for the long-term treatment of pathological hypersecretory conditions (e.g., Zollinger-Ellison syndrome, multiple endocrine adenomas and systemic mastocytosis).

CONTRAINDICATIONS
Omeprazole delayed-release capsules are contraindicated in patients with known hypersensitivity to any component of the formulation.

PRECAUTIONS

General
Symptomatic response to therapy with omeprazole does not preclude the presence of gastric malignancy.
Atrophic gastritis has been noted occasionally in gastric corpus biopsies from patients treated long-term with omeprazole.

Information for Patients
Omeprazole delayed-release capsules should be taken before eating. Patients should be cautioned that the omeprazole delayed-release capsule should not be opened, chewed or crushed, and should be swallowed whole.

For patients who have difficulty swallowing capsules, the contents of a omeprazole delayed-release capsule can be added to applesauce. One tablespoon of applesauce should be added to an empty bowl and the capsule should be opened. All of the pellets inside the capsule should be carefully emptied on the applesauce. The pellets should be mixed with the applesauce and then swallowed immediately with a glass of cool water to ensure complete swallowing of the pellets. The applesauce used should not be hot and should be soft enough to be swallowed without chewing. The pellets should not be chewed or crushed. The pellets/applesauce mixture should not be stored for future use.

Drug Interactions
Other
Omeprazole can prolong the elimination of diazepam, warfarin and phenytoin, drugs that are metabolized by oxidation in the liver. Although in normal subjects no interaction with theophylline or propranolol was found, there have been clinical reports of interaction with other drugs metabolized via the cytochrome P-450 system (e.g., cyclosporine, disulfiram, benzodiazepines). Patients should be monitored to determine if it is necessary to adjust the dosage of these drugs when taken concomitantly with omeprazole delayed-release capsules.

Because of its profound and long lasting inhibition of gastric acid secretion, it is theoretically possible that omeprazole may interfere with absorption of drugs where gastric pH is an important determinant of their bioavailability (e.g., ketoconazole, ampicillin esters, and iron salts). In the clinical trials, antacids were used concomitantly with the administration of omeprazole delayed-release capsules.

Carcinogenesis, Mutagenesis, Impairment of Fertility
In two 24-month carcinogenicity studies in [illegible] at daily doses of 1.7, 3.4,

Omeprazole can prolong the elimination of diazepam, warfarin and phenytoin, drugs that are metabolized by oxidation in the liver. Although in normal subjects no interaction with theophylline or propranolol was found, there have been clinical reports of interaction with other drugs metabolized via the cytochrome P-450 system (e.g., cyclosporine, disulfiram, benzodiazepines). Patients should be monitored to determine if it is necessary to adjust the dosage of these drugs when taken concomitantly with omeprazole delayed-release capsules.

Because of its profound and long lasting inhibition of gastric acid secretion, it is theoretically possible that omeprazole may interfere with absorption of drugs where gastric pH is an important determinant of their bioavailability (e.g., ketoconazole, ampicillin esters, and iron salts). In the clinical trials, antacids were used concomitantly with the administration of omeprazole delayed-release capsules.

Carcinogenesis, Mutagenesis, Impairment of Fertility

In two 24-month carcinogenicity studies in rats, omeprazole at daily doses of 1.7, 3.4, 13.8, 44.0 and 140.8 mg/kg/day (approximately 4 to 352 times the human dose, based on a patient weight of 50 kg and a human dose of 20 mg) produced gastric ECL cell carcinoids in a dose-related manner in both male and female rats; the incidence of this effect was markedly higher in female rats, which had higher blood levels of omeprazole. Gastric carcinoids seldom occur in the untreated rat. In addition, ECL cell hyperplasia was present in all treated groups of both sexes. In one of these studies, female rats were treated with 13.8 mg omeprazole/kg/day (approximately 35 times the human dose) for one year, then followed for an additional year without the drug. No carcinoids were seen in these rats. An increased incidence of treatment-related ECL cell hyperplasia was observed at the end of one year (94% treated vs 10% controls). By the second year the difference between treated and control rats was much smaller (46% vs 26%) but still showed more hyperplasia in the treated group. An unusual primary malignant tumor in the stomach was seen in one rat (2%). No similar tumor was seen in male or female rats treated for two years. For this strain of rat no similar tumor has been noted historically, but a finding involving only one tumor is difficult to interpret. A 78-week mouse carcinogenicity study of omeprazole did not show increased tumor occurrence, but the study was not conclusive.

Omeprazole was not mutagenic in an *in vitro* Ames *Salmonella typhimurium* assay, an *in vitro* mouse lymphoma cell assay and an *in vivo* rat liver DNA damage assay. A mouse micronucleus test at 625 and 6250 times the human dose gave a borderline result, as did an *in vivo* bone marrow chromosome aberration test. A second mouse micronucleus study at 2000 times the human dose, but with different (suboptimal) sampling times, was negative.

In a rat fertility and general reproductive performance test, omeprazole in a dose range of 13.8 to 138.0 mg/kg/day (approximately 35 to 345 times the human dose) was not toxic or deleterious to the reproductive performance of parental animals.

Pregnancy

Pregnancy Category C: Teratology studies conducted in pregnant rats at doses up to 138 mg/kg/day (approximately 345 times the human dose) and in pregnant rabbits at doses up to 69 mg/kg/day (approximately 172 times the human dose) did not disclose any evidence for a teratogenic potential of omeprazole.

In rabbits, omeprazole in a dose range of 6.9 to 69.1 mg/kg/day (approximately 17 to 172 times the human dose) produced dose-related increases in embryo-lethality, fetal resorptions and pregnancy disruptions. In rats, dose-related embryo/fetal toxicity and postnatal developmental toxicity were observed in offspring resulting from parents treated with omeprazole 13.8 to 138.0 mg/kg/day (approximately 35 to 345 times the human dose). There are no adequate or well-controlled studies in pregnant women. Sporadic reports have been received of congenital abnormalities occurring in infants born to women who have received omeprazole during pregnancy. Omeprazole should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

It is not known whether omeprazole is excreted in human milk. In rats, omeprazole administration during late gestation and lactation at doses of 13.8 to 138 mg/kg/day (35 to 345 times the human dose) resulted in decreased weight gain in pups. Because many drugs are excreted in human milk, because of the potential for serious adverse reactions in nursing infants from omeprazole, and because of the potential for tumorigenicity shown for omeprazole in rat carcinogenicity studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Omeprazole was administered to over 2000 elderly individuals (>65 years of age) in clinical trials in the US and Europe. There were no differences in safety and effectiveness between the elderly and younger subjects. Other reported clinical experience has not identified differences in response between the elderly and younger subjects, but greater sensitivity of some older individuals cannot be ruled out.

Pharmacokinetic studies have shown the elimination rate was somewhat decreased in elderly and bioavailability was increased. The plasma clearance of omeprazole was 250 mL/min (about half that of young volunteers) and its plasma half-life averaged one hour, about twice that of young healthy volunteers. However, no dosage adjustment is necessary in the elderly. (See CLINICAL PHARMACOLOGY.)

ADVERSE REACTIONS

Omeprazole delayed-release capsules were generally well tolerated during domestic and international clinical trials in 3096 patients.

In the U.S. clinical trial population of 465 patients (including duodenal ulcer, Zollinger-Ellison syndrome and resistant ulcer patients), the following adverse experiences were reported to occur in 1% or more of patients on therapy with omeprazole delayed-release capsules. Numbers in parentheses indicate percentages of the adverse experiences considered by investigators as possibly, probably or definitely related to the drug:

	Omeprazole (n = 465)	Placebo (n = 64)	Ranitidine (n = 195)
Headache	6.9 (2.4)	6.3	7.7 (2.6)
Diarrhea	3.0 (1.9)	3.1 (1.6)	2.1 (0.5)
Abdominal Pain	2.4 (0.4)	3.1	2.1
Nausea			

cal trials in the US and Europe. There were no differences in safety and effectiveness between the elderly and younger subjects. Other reported clinical experience has not identified differences in response between the elderly and younger subjects, but greater sensitivity of some older individuals cannot be ruled out.

Pharmacokinetic studies have shown the elimination rate was somewhat decreased in elderly and bioavailability was increased. The plasma clearance of omeprazole was 250 mL/min (about half that of young volunteers) and its plasma half-life averaged one hour, about twice that of young healthy volunteers. However, no dosage adjustment is necessary in the elderly. (See CLINICAL PHARMACOLOGY.)

ADVERSE REACTIONS

Omeprazole delayed-release capsules were generally well tolerated during domestic and international clinical trials in 3096 patients.

In the U.S. clinical trial population of 465 patients (including duodenal ulcer, Zollinger-Ellison syndrome and resistant ulcer patients), the following adverse experiences were reported to occur in 1% or more of patients on therapy with omeprazole delayed-release capsules. Numbers in parentheses indicate percentages of the adverse experiences considered by investigators as possibly, probably or definitely related to the drug:

	Omeprazole (n = 465)	Placebo (n = 64)	Ranitidine (n = 195)
Headache	6.9 (2.4)	6.3	7.7 (2.6)
Diarrhea	3.0 (1.9)	3.1 (1.6)	2.1 (0.5)
Abdominal Pain	2.4 (0.4)	3.1	2.1
Nausea	2.2 (0.9)	3.1	4.1 (0.5)
URI	1.9	1.6	2.6
Dizziness	1.5 (0.6)	0.0	2.6 (1.0)
Vomiting	1.5 (0.4)	4.7	1.5 (0.5)
Rash	1.5 (1.1)	0.0	0.0
Constipation	1.1 (0.9)	0.0	0.0
Cough	1.1	0.0	1.5
Asthenia	1.1 (0.2)	1.6 (1.6)	1.5 (1.0)
Back Pain	1.1	0.0	0.5

The following adverse reactions which occurred in 1% or more of omeprazole-treated patients have been reported in international double-blind, and open-label, clinical trials in which 2,631 patients and subjects received omeprazole.

Incidence of Adverse Experiences ≥1%
Causal Relationship Not Assessed

Body as a Whole, site unspecified	Omeprazole (n = 2631)	Placebo (n = 120)
Abdominal pain	5.2	3.3
Asthenia	1.3	0.8
Digestive System		
Constipation	1.5	0.8
Diarrhea	3.7	2.5
Flatulence	2.7	5.8
Nausea	4.0	6.7
Vomiting	3.2	10.0
Acid regurgitation	1.9	3.3
Nervous System/ Psychiatric		
Headache	2.9	2.5

Additional adverse experiences occurring in <1% of patients or subjects in domestic and/or international trials, or occurring since the drug was marketed, are shown below within each body system. In many instances, the relationship to omeprazole delayed-release capsules was unclear.

Body As a Whole: Allergic reactions, including, rarely, anaphylaxis (see also Skin below), fever, pain, fatigue, malaise, abdominal swelling.

Cardiovascular: Chest pain or angina, tachycardia, bradycardia, palpitation, elevated blood pressure, peripheral edema.

Gastrointestinal: Pancreatitis (some fatal), anorexia, irritable colon, flatulence, fecal discoloration, esophageal candidiasis, mucosal atrophy of the tongue, dry mouth. During treatment with omeprazole, gastric fundic gland polyps have been noted rarely. These polyps are benign and appear to be reversible when treatment is discontinued.

Gastro-duodenal carcinoids have been reported in patients with ZE syndrome on long-term treatment with omeprazole delayed-release capsules. This finding is believed to be a manifestation of the underlying condition, which is known to be associated with such tumors.

Hepatic: Mild and, rarely, marked elevations of liver function tests [ALT (SGPT), AST (SGOT), (γ-glutamyl transpeptidase, alkaline phosphatase, and bilirubin (jaundice)]. In rare instances, overt liver disease has occurred, including hepatocellular, cholestatic, or mixed hepatitis, liver necrosis (some fatal), hepatic failure (some fatal), and hepatic encephalopathy.

Metabolic/Nutritional: Hyponatremia, hypoglycemia, weight gain.

Musculoskeletal: Muscle cramps, myalgia, muscle weakness, joint pain, leg pain.

Nervous System/Psychiatric: Psychic disturbances including depression, aggression, hallucinations, confusion, insomnia, nervousness, tremors, apathy, somnolence, anxiety, dream abnormalities; vertigo; paresthesia; hemifacial dysesthesia.

Respiratory: Epistaxis, pharyngeal pain.

Skin: Rash and, rarely, cases of severe generalized skin reactions including toxic epidermal necrolysis (TEN; some fatal), Stevens-Johnson syndrome, and erythema multiforme (some severe); purpura and/or petechiae (some with rechallenge); skin inflammation; urticaria, angioedema, pruritus, alopecia, dry skin, hyperhidrosis.

Special Senses: Tinnitus, taste perversion.

Urogenital: Interstitial nephritis (some with positive rechallenge), urinary tract infection, microscopic pyuria, urinary frequency, elevated serum creatinine, proteinuria, hematuria, glycosuria, testicular pain, gynecomastia.

Hematologic: Rare instances of pancytopenia, agranulocytosis (some fatal), thrombocytopenia, neutropenia, anemia, leucocytosis, and hemolytic anemia have been reported.

The incidence of clinical adverse experiences in patients greater than 65 years of age was similar to that in patients 65 years of age or less.

OVERDOSAGE

Rare reports have been received of overdosage with omeprazole. Doses ranged from 320 mg to 900 mg (16 to 45 times the usual recommended clinical dose). Manifestations were variable, but included confusion, drowsiness, blurred vision, tachycardia, nausea, diaphoresis, flushing, headache, and dry mouth. Symptoms were transient, and no serious clinical outcome has been reported.

No specific antidote for omeprazole overdosage is known. Omeprazole is extensively protein bound and is, therefore, not readily dialyzable. In the event of overdosage, treatment should be symptomatic and supportive.

Lethal doses of omeprazole after single oral administration are about 1500 mg/kg in mice and greater than 4000 mg/kg in rats, and about 100 mg/kg in mice and greater than

Metabolic/Nutritional: Hyponatremia, hypoglycemia, weight gain.

Musculoskeletal: Muscle cramps, myalgia, muscle weakness, joint pain, leg pain.

Nervous System/Psychiatric: Psychic disturbances including depression, aggression, hallucinations, confusion, insomnia, nervousness, tremors, apathy, somnolence, anxiety, dream abnormalities; vertigo; paresthesia; hemifacial dysesthesia.

Respiratory: Epistaxis, pharyngeal pain.

Skin: Rash and, rarely, cases of severe generalized skin reactions including toxic epidermal necrolysis (TEN; some fatal), Stevens-Johnson syndrome, and erythema multiforme (some severe); purpura and/or petechiae (some with rechallenge); skin inflammation, urticaria, angioedema, pruritus, alopecia, dry skin, hyperhidrosis.

Special Senses: Tinnitus, taste perversion.

Urogenital: Interstitial nephritis (some with positive rechallenge), urinary tract infection, microscopic pyuria, urinary frequency, elevated serum creatinine, proteinuria, hematuria, glycosuria, testicular pain, gynecomastia.

Hematologic: Rare instances of pancytopenia, agranulocytosis (some fatal), thrombocytopenia, neutropenia, anemia, leucocytosis, and hemolytic anemia have been reported.
The incidence of clinical adverse experiences in patients greater than 65 years of age was similar to that in patients 65 years of age or less.

OVERDOSAGE

Rare reports have been received of overdosage with omeprazole. Doses ranged from 320 mg to 900 mg (16 to 45 times the usual recommended clinical dose). Manifestations were variable, but included confusion, drowsiness, blurred vision, tachycardia, nausea, diaphoresis, flushing, headache, and dry mouth. Symptoms were transient, and no serious clinical outcome has been reported. No specific antidote for omeprazole overdosage is known. Omeprazole is extensively protein bound and is, therefore, not readily dialyzable. In the event of overdosage, treatment should be symptomatic and supportive. Lethal doses of omeprazole after single oral administration are about 1500 mg/kg in mice and greater than 4000 mg/kg in rats, and about 100 mg/kg in mice and greater than 40 mg/kg in rats given single intravenous injections. Animals given these doses showed sedation, ptosis, convulsions, and decreased activity, body temperature, and respiratory rate and increased depth of respiration.

DOSAGE AND ADMINISTRATION

Short-Term Treatment of Active Duodenal Ulcer
Short-Term Treatment of Active Duodenal Ulcer: The recommended adult oral dose of omeprazole delayed-release capsules is 20 mg once daily. Most patients heal within four weeks. Some patients may require an additional four weeks of therapy. (See INDICATIONS AND USAGE.)

Gastric Ulcer
The recommended adult oral dose is 40 mg once a day for 4 to 8 weeks. (See CLINICAL PHARMACOLOGY, *Clinical Studies, Gastric Ulcer*, and INDICATIONS AND USAGE, *Gastric Ulcer.*)

Gastroesophageal Reflux Disease (GERD)
The recommended adult oral dose for the treatment of patients with symptomatic GERD and no esophageal lesions is 20 mg daily for up to 4 weeks. The recommended adult oral dose for the treatment of patients with erosive esophagitis and accompanying symptoms due to GERD is 20 mg daily for 4 to 8 weeks. (See INDICATIONS AND USAGE).

Maintenance of Healing of Erosive Esophagitis
The recommended adult oral dose is 20 mg daily. (See CLINICAL PHARMACOLOGY, *Clinical Studies.*)

Pathological Hypersecretory Conditions
The dosage of omeprazole delayed-release capsules in patients with pathological hypersecretory conditions varies with the individual patient. The recommended adult oral starting dose is 60 mg once a day. Doses should be adjusted to individual patient needs and should continue for as long as clinically indicated. Doses up to 120 mg t.i.d. have been administered. Daily dosages of greater than 80 mg should be administered in divided doses. Some patients with Zollinger-Ellison syndrome have been treated continuously with omeprazole delayed-release capsules for more than 5 years.
No dosage adjustment is necessary for patients with renal impairment, hepatic dysfunction or for the elderly.
Omeprazole delayed-release capsules should be taken before eating. In the clinical trials, antacids were used concomitantly with omeprazole delayed-release capsules.
Patients should be cautioned that the omeprazole delayed-release capsule should not be opened, chewed or crushed, and should be swallowed whole.
For patients who have difficulty swallowing capsules, the contents of a omeprazole delayed-release capsule can be added to applesauce. One tablespoon of applesauce should be added to an empty bowl and the capsule should be opened. All of the pellets inside the capsule should be carefully emptied on the applesauce. The pellets should be mixed with the applesauce and then swallowed immediately with a glass of cool water to ensure complete swallowing of the pellets. The applesauce used should not be hot and should be soft enough to be swallowed without chewing. The pellets should not be chewed or crushed. The pellets/applesauce mixture should not be stored for future use.

HOW SUPPLIED

Omeprazole Delayed-release Capsules, 10 mg, are opaque, hard gelatin, light green and white colored capsules, imprinted "Andrx 610" on the cap and "10 mg" on the body. They are supplied as follows:
NDC 62037-610-07 sample bottles of 7
NDC 62037-610-30 unit of use bottles of 30
NDC 62037-610-10 bottles of 1000

Omeprazole Delayed-release Capsules, 20 mg, are opaque, hard gelatin, dark green and white colored capsules, imprinted "Andrx 620" on the cap and "20 mg" on the body. They are supplied as follows:
NDC 62037-620-07 sample bottles of 7
NDC 62037-620-30 unit of use bottles of 30
NDC 62037-620-10 bottles of 1000

Omeprazole Delayed-release Capsules, 40 mg, are opaque, hard gelatin, dark green and light green colored capsules, imprinted "Andrx 640" on the cap and "40 mg" on the body. They are supplied as follows:
NDC 62037-640-07 sample bottles of 7
NDC 62037-640-30 unit of use bottles of 30
NDC 62037-640-10 bottles of 1000

Storage
Store Omeprazole Delayed-release Capsules in a tight container protected from light and moisture. Store between 15°C and 30°C (59°F

dose for the treatment of patients with erosive esophagitis and accompanying symptoms due to GERD is 20 mg daily for 4 to 8 weeks. (See INDICATIONS AND USAGE).

Maintenance of Healing of Erosive Esophagitis
The recommended adult oral dose is 20 mg daily. (See CLINICAL PHARMACOLOGY, *Clinical Studies*.)

Pathological Hypersecretory Conditions
The dosage of omeprazole delayed-release capsules in patients with pathological hypersecretory conditions varies with the individual patient. The recommended adult oral starting dose is 60 mg once a day. Doses should be adjusted to individual patient needs and should continue for as long as clinically indicated. Doses up to 120 mg t.i.d. have been administered. Daily dosages of greater than 80 mg should be administered in divided doses. Some patients with Zollinger-Ellison syndrome have been treated continuously with omeprazole delayed-release capsules for more than 5 years.
No dosage adjustment is necessary for patients with renal impairment, hepatic dysfunction or for the elderly.
Omeprazole delayed-release capsules should be taken before eating. In the clinical trials, antacids were used concomitantly with omeprazole delayed-release capsules.
Patients should be cautioned that the omeprazole delayed-release capsule should not be opened, chewed or crushed, and should be swallowed whole.
For patients who have difficulty swallowing capsules, the contents of a omeprazole delayed-release capsule can be added to applesauce. One tablespoon of applesauce should be added to an empty bowl and the capsule should be opened. All of the pellets inside the capsule should be carefully emptied on the applesauce. The pellets should be mixed with the applesauce and then swallowed immediately with a glass of cool water to ensure complete swallowing of the pellets. The applesauce used should not be hot and should be soft enough to be swallowed without chewing. The pellets should not be chewed or crushed. The pellets/applesauce mixture should not be stored for future use.

HOW SUPPLIED
Omeprazole Delayed-release Capsules, 10 mg, are opaque, hard gelatin, light green and white colored capsules, imprinted "Andrx 610" on the cap and "10 mg" on the body. They are supplied as follows:
NDC 62037-610-07 sample bottles of 7
NDC 62037-610-30 unit of use bottles of 30
NDC 62037-610-10 bottles of 1000

Omeprazole Delayed-release Capsules, 20 mg, are opaque, hard gelatin, dark green and white colored capsules, imprinted "Andrx 620" on the cap and "20 mg" on the body. They are supplied as follows:
NDC 62037-620-07 sample bottles of 7
NDC 62037-620-30 unit of use bottles of 30
NDC 62037-620-10 bottles of 1000

Omeprazole Delayed-release Capsules, 40 mg, are opaque, hard gelatin, dark green and light green colored capsules, imprinted "Andrx 640" on the cap and "40 mg" on the body. They are supplied as follows:
NDC 62037-640-07 sample bottles of 7
NDC 62037-640-30 unit of use bottles of 30
NDC 62037-640-10 bottles of 1000

Storage
Store Omeprazole Delayed-release Capsules in a tight container protected from light and moisture. Store between 15°C and 30°C (59°F and 86°F)

Manufactured by:
Andrx Pharmaceuticals, Inc.
Ft. Lauderdale, FL 33314

Rev. 10/01 7062

Andrx
PHARMACEUTICALS, INC.

NDC 62037-640-10

NOV 16 2001
APPROVED

OMEPRAZOLE

DELAYED-RELEASE CAPSULES

40 mg

Rx ONLY

1000 Capsules

Usual adult dosage: See accompanying information.
Dispense in a tight, light-resistant container.
Protect from moisture.
Store between 15°C and 30°C (59°F and 86°F).
The Omeprazole Delayed-release Capsule should be swallowed whole, and not opened, chewed, or crushed.

Manufactured by:
Andrx Pharmaceuticals, Inc.
Fort Lauderdale, FL 33314

7061 (01/01)

N 3 62037-640-10 0

UNMARKED AREA

LOT:
EXP.:

CHECK ARTWORK CAREFULLY !!!!	Write ALL corrections on artwork. Once this is signed, you will be responsible for any mistakes on artwork, typesetting or color. NOTE: Artwork is billed on a time basis. All corrections or revisions are billed at half hour increments (Excluding errors incurred by Blue Ribbon Tag & Label).		
JOB 01-1441	DATE 03/08/01	CUST. ANDRX	
SIZE 8"x3.4375"	COLORS PMS 021, 199, BLACK		
ART BY SC	BLUE RIBBON TAG & LABEL CORP.	PROOF # 1	

NOTE: COLOR PROOFS ARE PROVIDED ONLY AS A VISUAL REFERENCE TO THE FINAL PRINTED PIECE. THE COLORS SHOWN ARE ONLY REPRESENTATIONAL, AND ARE NOT INTENDED TO MATCH ACTUAL PRESS COLORS.

PROOFREADING
This proof was compared to:
☐ Customer supplied text
☐ Existing/Printed label
☐ Customer revisions AND previous proof
by: _____

ap 11/16/01
75-347

Andrx
PHARMACEUTICALS, INC.

NOV 16 2001

NDC 62037-620-10

APPROVED

OMEPRAZOLE

DELAYED-RELEASE CAPSULES

20 mg

Rx ONLY

1000 Capsules

Usual adult dosage: See accompanying information.
Dispense in a tight, light-resistant container.
Protect from moisture.
Store between 15°C and 30°C (59°F and 86°F).
The Omeprazole Delayed-release Capsule should be swallowed whole, and not opened, chewed, or crushed.

Manufactured by:
Andrx Pharmaceuticals, Inc.
Fort Lauderdale, FL 33314

7058 (01/01)

N 3 62037-620-10 2

LOT:

EXP.:

CHECK ARTWORK CAREFULLY !!!! Write ALL corrections on artwork. Once this is signed, you will be responsible for any mistakes on artwork, typesetting or color. NOTE: Artwork is billed on a time basis. All corrections or revisions are billed at half hour increments (Excluding errors incurred by Blue Ribbon Tag & Label).				NOTE: COLOR PROOFS ARE PROVIDED ONLY AS A VISUAL REFERENCE TO THE FINAL PRINTED PIECE. THE COLORS SHOWN ARE ONLY REPRESENTATIONAL, AND ARE NOT INTENDED TO MATCH ACTUAL PRESS COLORS.
JOB 01-1230	DATE 04/10/01	CUST. ANDRX	NOV 16 2001	
SIZE 8" x3.4375"	COLORS PMS 199, 347C, Black			
ART BY SC	BLUE RIBBON TAG & LABEL CORP.	PROOF # 1		

Proofread by: _____

Compared to:
- ☐ Customer supplied proof
- ☐ Existing/Printed Label
- ☐ Printout from Cust Disk.
- ☐ Proof # _____

Andrx
PHARMACEUTICALS, INC.

APPROVED
NOV 16 2001

[redacted]

OMEPRAZOLE

DELAYED-RELEASE CAPSULES

10 mg

Rx ONLY

1000 Capsules

Usual adult dosage: See accompanying information.
Dispense in a tight, light-resistant container.
Protect from moisture.
Store between 15°C and 30°C (59°F and 86°F).
The Omeprazole Delayed-release Capsule should be swallowed whole, and not opened, chewed, or crushed.

Manufactured by:
Andrx Pharmaceuticals, Inc.
Fort Lauderdale, FL 33314

7055 (12/00)

N 3 62037-610-10 3

UNVARNISHED AREA
1" x 2"

LOT:

EXP.:

CHECK ARTWORK CAREFULLY !!!!	Write ALL corrections on artwork. Once this is signed, you will be responsible for any mistakes on artwork, typesetting or color. NOTE: Artwork is billed on a time basis. All corrections or revisions are billed at half hour increments (Excluding errors incurred by Blue Ribbon Tag & Label).		
JOB 01-1555	DATE 03/14/01	CUST. ANDRX	
SIZE 8"x3.4375"	COLORS PMS 072, 199, BLACK	NOV 16 2001	
ART BY SC	BLUE RIBBON TAG & LABEL CORP.	PROOF # 1	

NOTE: COLOR PROOFS ARE PROVIDED ONLY AS A VISUAL REFERENCE TO THE FINAL PRINTED PIECE. THE COLORS SHOWN ARE ONLY REPRESENTATIONAL, AND ARE NOT INTENDED TO MATCH ACTUAL PRESS COLORS.

PROOFREADING
This proof was compared to:
☐ Customer supplied text
☐ Existing/Printed label
☐ Customer revisions AND previous proof

by: _____

Andrx
PHARMACEUTICALS, INC.

NDC 62037-640-30

OMEPRAZOLE

DELAYED-RELEASE CAPSULES

40 mg

Rx ONLY

30 Capsules

Usual adult dosage: See accompanying information.

Keep container tightly closed.

Protect from light and moisture.

Store between 15°C and 30°C (59°F and 86°F).

The Omeprazole Delayed-release Capsule should be swallowed whole, and not opened, chewed, or crushed.

Manufactured by:
Andrx Pharmaceuticals, Inc.
Fort Lauderdale, FL 33314

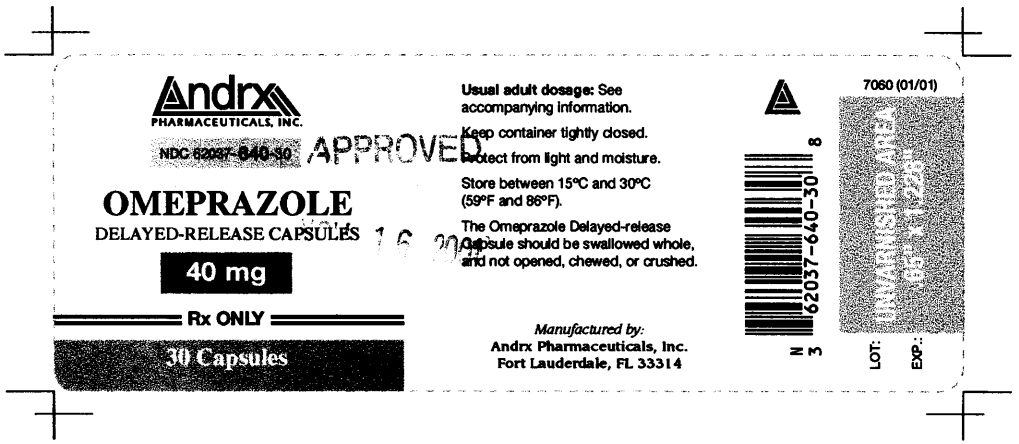
7060 (01/01)

N 3 62037-640-30 8

UNVARNISHED AREA
.65" x 1.228"

LOT:

EXP.:



CHECK ARTWORK CAREFULLY !!!! Write ALL corrections on artwork. Once this is signed, you will be responsible for any mistakes on artwork, typesetting or color. NOTE: Artwork is billed on a time basis. All corrections or revisions are billed at half hour increments (Excluding errors incurred by Blue Ribbon Tag & Label).			
JOB 01-1232	DATE 03/14/01	CUST. ANDRX	
SIZE 4.75"X1.75"	COLORS PMS 021, PMS 199, PMS BLACK		
ART BY SC	BLUE RIBBON TAG & LABEL CORP.	PROOF # 2	

NOTE: COLOR PROOFS ARE PROVIDED ONLY AS A VISUAL REFERENCE TO THE FINAL PRINTED PIECE. THE COLORS SHOWN ARE ONLY REPRESENTATIONAL, AND ARE NOT INTENDED TO MATCH ACTUAL PRESS COLORS.

PROOFREADING
This proof was compared to:
- ☐ Customer supplied text
- ☐ Existing/Printed label
- ☐ Customer revisions AND previous proof

by: _____

Andrx
PHARMACEUTICALS, INC.

NDC 62037-620-30

OMEPRAZOLE
DELAYED-RELEASE CAPSULES

20 mg

Rx ONLY

Usual adult dosage: See accompanying information.

Keep container tightly closed.

Protect from light and moisture.

Store between 15°C and 30°C (59°F and 86°F).

The Omeprazole Delayed-release Capsule should be swallowed whole, and not opened, chewed, or crushed.

7057 (01/01)

Manufactured by:
Andrx Pharmaceuticals, Inc.
Fort Lauderdale, FL 33314

NOV 16 2001

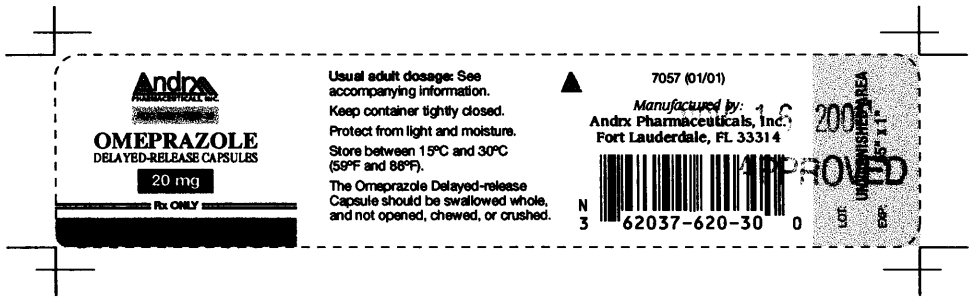
APPROVED

N 3 62037-620-30 0

UNVARNISHED AREA .55" x 1"

LOT:

EXP:



CHECK ARTWORK CAREFULLY !!!!	Write ALL corrections on artwork. Once this is signed, you will be responsible for any mistakes on artwork, typesetting or color. NOTE: Artwork is billed on a time basis. All corrections or revisions are billed at half hour increments (Excluding errors incurred by Blue Ribbon Tag & Label)		
JOB 01-1229	DATE 03/14/01	CUST. ANDRX	APPROVED NOV 16 2001
SIZE 4.5"X1"	COLORS PMS 347, PMS 199, PMS BLACK		
ART BY SC	BLUE RIBBON TAG & LABEL CORP.	PROOF # 2	

NOTE: COLOR PROOFS ARE PROVIDED ONLY AS A VISUAL REFERENCE TO THE FINAL PRINTED PIECE. THE COLORS SHOWN ARE ONLY REPRESENTATIONAL, AND ARE NOT INTENDED TO MATCH ACTUAL PRESS COLORS.

PROOFREADING
This proof was compared to:
- ☐ Customer supplied text
- ☐ Existing/Printed label
- ☐ Customer revisions AND previous proof

by: _____

Andrx PHARMACEUTICALS, INC.

OMEPRAZOLE

DELAYED-RELEASE CAPSULES

10 mg

Rx ONLY

Usual adult dosage: See accompanying information.

Keep container tightly closed.

Protect from light and moisture.

Store between 15°C and 30°C (59°F and 86°F).

The Omeprazole Delayed-release Capsule should be swallowed whole, and not opened, chewed, or crushed.

7054 (01/01)

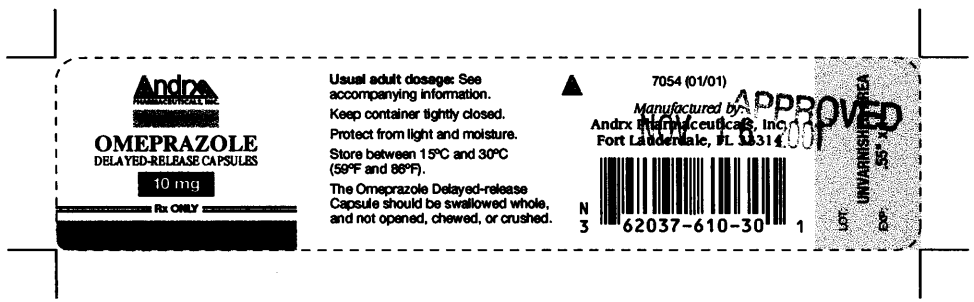
APPROVED

NOV 19 2001

Manufactured by:
Andrx Pharmaceuticals, Inc.
Fort Lauderdale, FL 33314

N 3 62037-610-30 1

LOT: UNVARNISHED AREA EXP: .55" x 1"



CHECK ARTWORK CAREFULLY !!!!	Write ALL corrections on artwork. Once this is signed, you will be responsible for any mistakes on artwork, typesetting or color. NOTE: Artwork is billed on a time basis. All corrections or revisions are billed at half hour increments (Excluding errors incurred by Blue Ribbon Tag & Label).			NOTE: COLOR PROOFS ARE PROVIDED ONLY AS A VISUAL REFERENCE TO THE FINAL PRINTED PIECE. THE COLORS SHOWN ARE ONLY REPRESENTATIONAL, AND ARE NOT INTENDED TO MATCH ACTUAL PRESS COLORS.
JOB 00-1552	DATE 03/14/01	CUST. ANDRX	NOV	
SIZE 4.5" x 1"	COLORS PMS 199, 072C, Black			
ART BY SC	BLUE RIBBON TAG & LABEL CORP.	PROOF # 7		

Proofread by: _____

Compared to:
- ☐ Customer supplied proof
- ☐ Existing/Printed Label
- ☐ Printout from Cust Disk.
- ☐ Proof # _____

Andrx
PHARMACEUTICALS, INC.

NDC 62037-640-07

OMEPRAZOLE
DELAYED-RELEASE CAPSULES

40 mg

Rx ONLY

Usual adult dosage: See accompanying information.

Keep container tightly closed.

Protect from light and moisture.

Store between 15°C and 30°C (59°F and 86°F).

The Omeprazole Delayed-release Capsule should be swallowed whole, and not opened, chewed, or crushed.

7059 (01/01)

Manufactured by:
Andrx Pharmaceuticals, Inc.
Fort Lauderdale, FL 33314

NOV 16 2001

APPROVED

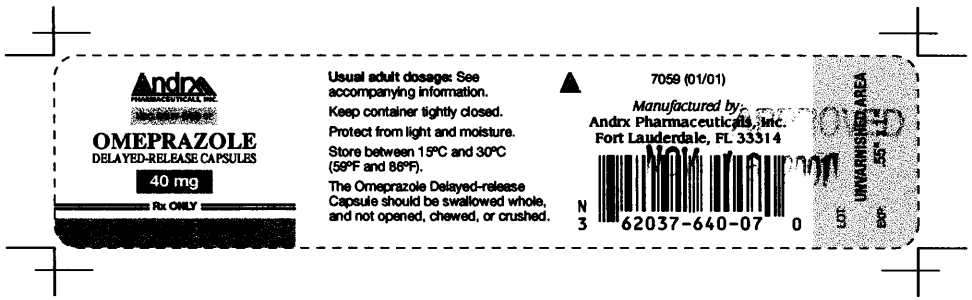
N 3 62037-640-07 0

LOT:

UNVARNISHED AREA

EXP:

.55" x 1"



CHECK ARTWORK CAREFULLY !!!! Write ALL corrections on artwork. Once this is signed, you will be responsible for any mistakes on artwork, typesetting or color. NOTE: Artwork is billed on a time basis. All corrections or revisions are billed at half hour increments (Excluding errors incurred by Blue Ribbon Tag & Label).

JOB 01-1231	DATE 03/17/01	CUST. ANDRX	
SIZE 4.5"X1"	COLORS PMS 021, PMS 199, PMS BLACK		
ART BY SC	BLUE RIBBON TAG & LABEL CORP.	PROOF # 3	

NOTE: COLOR PROOFS ARE PROVIDED ONLY AS A VISUAL REFERENCE TO THE FINAL PRINTED PIECE. THE COLORS SHOWN ARE ONLY REPRESENTATIONAL, AND ARE NOT INTENDED TO MATCH ACTUAL PRESS COLORS.

NOV 16 2001

PROOFREADING
This proof was compared to:
- ☐ Customer supplied text
- ☐ Existing/Printed label
- ☐ Customer revisions AND previous proof

by: _____

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-347

CHEMISTRY REVIEW(S)

1. CHEMIST'S REVIEW **#1**

2. ANDA **#75-347**

3. NAME AND ADDRESS OF APPLICANT
Andrx Pharmaceuticals, Inc.
4001 S.W. 47th Avenue
Fort Lauderdale, FL 33314

4. LEGAL BASIS FOR ANDA SUBMISSION
Andrx Pharmaceuticals' proposed drug product, Omeprazole Delayed-release Capsules, 10 mg and 20 mg, is suitable for an Abbreviated New Drug Application on the basis that it is the same as the reference listed drug. The reference listed drug is Prilosec, Delayed-release capsule.

5. SUPPLEMENT(S)
N/A

6. PROPRIETARY NAME
Prilosec DRC®

7. NONPROPRIETARY NAME
Omeprazole

9. AMENDMENTS AND OTHER DATES:
Labeling amendment 4/9/98

10. PHARMACOLOGICAL CATEGORY
Gastric acid pump inhibitor

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)
DMF

13. DOSAGE FORM
Delayed release capsule

14. POTENCY
10 mg & 20 mg

15. CHEMICAL NAME AND STRUCTURE
5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1*H*-benzimidazole

16. RECORDS AND REPORTS

Redacted 21

pages of

trade secret and/or

confidential

commercial

information

1. CHEMIST'S REVIEW **#2**

2. ANDA **#75-347**

3. NAME AND ADDRESS OF APPLICANT
Andrx Pharmaceuticals, Inc.
4001 S.W. 47th Avenue
Fort Lauderdale, FL 33314

4. LEGAL BASIS FOR ANDA SUBMISSION
Andrx Pharmaceuticals' proposed drug product, Omeprazole Delayed-release Capsules, 10 mg and 20 mg, is suitable for an Abbreviated New Drug Application on the basis that it is the same as the reference listed drug. The reference listed drug is Prilosec, Delayed-release capsule. The following patents cover the RLD: 4,786,505 (expiry date 3/22/1999), 4,636,499 (expiry date 5/30/2005), 4,255,431 (expired on 6/22/98), 4,853,230 (expiry date 4/20/2007), 5,093,342 (2/2/2010), 5,599,794 (2/4/2014) and 5,629,305 (2/4/2014). The firm has filed a Paragraph IV certification against all of the patents except 4,255,431.

5. SUPPLEMENT(S)
N/A

6. PROPRIETARY NAME
Prilosec DRC®

7. NONPROPRIETARY NAME
Omeprazole

9. AMENDMENTS AND OTHER DATES:
Firm
Date filed: 3/17/98
Label amendment: 4/09/98
Bio amendment: 4/17/98
New correspondence: 5/28/98
New Correspondence: 5/29/98
Major amendment: 8/5/98
Bio Telephone amendment: 8/14/98
40 mg Strength amendment: 9/28/98

FDA
Communication with ANDA filing date: 4/7/98
CMC Deficiency letter out: 7/20/98
Labeling comments out: 8/18/98
Bio sign off on approval: 8/24/98
Label deficiencies: 11/9/98

10. PHARMACOLOGICAL CATEGORY
Gastric acid pump inhibitor

11 Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

DMF [redacted]

13. DOSAGE FORM
Delayed-release capsule

14. POTENCY
10 mg, 20 mg & 40 mg

15. CHEMICAL NAME AND STRUCTURE
5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1*H*-benzimidazole

16. RECORDS AND REPORTS
NA

17. COMMENTS
See review.

18. CONCLUSIONS AND RECOMMENDATIONS
Not Approvable, facsimile.

19. REVIEWER
Radhika Rajagopalan, Ph.D.

DATE COMPLETED
November 9, 1998; 12/3/98

Redacted 22

pages of

trade secret and/or

confidential

commercial

information

1. CHEMIST'S REVIEW #3

2. ANDA #75-347

3. NAME AND ADDRESS OF APPLICANT
Andrx Pharmaceuticals, Inc.
4001 S.W. 47th Avenue
Fort Lauderdale, FL 33314

4. LEGAL BASIS FOR ANDA SUBMISSION
Andrx Pharmaceuticals' proposed drug product, Omeprazole Delayed-release Capsules, 10 mg and 20 mg, is suitable for an Abbreviated New Drug Application on the basis that it is the same as the reference listed drug. The reference listed drug is Prilosec, Delayed-release capsule. The following patents cover the RLD: 4,786,505 (expiry date 3/22/1999), 4,636,499 (expiry date 5/30/2005), 4,255,431 (expired on 6/22/98), 4,853,230 (expiry date 4/20/2007), 5,093,342 (2/2/2010), 5,599,794 (2/4/2014) and 5,629,305 (2/4/2014). The firm has filed a Paragraph IV certification against all of the patents except 4,255,431.

5. SUPPLEMENT(S)
N/A

6. PROPRIETARY NAME
Prilosec DRC®

7. NONPROPRIETARY NAME
Omeprazole

9. AMENDMENTS AND OTHER DATES:
Firm
Date filed: 3/17/98
Label amendment: 4/13/98
Bio amendment: 4/17/98
New correspondence: 5/28/98
New Correspondence: 5/29/98
Major amendment: 8/5/98
Bio Telephone amendment: 8/14/98
40 mg Strength amendment: 9/28/98
Facsimile amendment: 12/23/98

FDA
Communication with ANDA filing date: 4/7/98
CMC Deficiency letter out: 7/20/98
Labeling comments out: 8/18/98
Bio sign off on approval: 8/24/98
Label deficiencies: 11/9/98
Chemistry deficiencies faxed: 12/11/98
Phone call by P. Rickman: 12/22/98
Bio Waiver for 40 mg: 1/11/99

10. PHARMACOLOGICAL CATEGORY
Gastric acid pump inhibitor

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)
DMF [redacted]

13. DOSAGE FORM
Delayed-release capsule

14. POTENCY
10 mg, 20 mg & 40 mg

15. CHEMICAL NAME AND STRUCTURE
5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1*H*-benzimidazole

16. RECORDS AND REPORTS
NA

17. COMMENTS
Facsimile amendment is required.

18. CONCLUSIONS AND RECOMMENDATIONS
Not approvable.

19. REVIEWER
Radhika Rajagopalan, Ph.D.

DATE COMPLETED
February 4, 1999

Redacted 21

pages of

trade secret and/or

confidential

commercial

information

1. CHEMIST'S REVIEW **#4**

2. ANDA **#75-347**

3. NAME AND ADDRESS OF APPLICANT
Andrx Pharmaceuticals, Inc.
4001 S.W. 47th Avenue
Fort Lauderdale, FL 33314

4. LEGAL BASIS FOR ANDA SUBMISSION
Andrx Pharmaceuticals' proposed drug product, Omeprazole Delayed-release Capsules, 10 mg and 20 mg, is suitable for an Abbreviated New Drug Application on the basis that it is the same as the reference listed drug. The reference listed drug is Prilosec, Delayed-release capsule. The following patents cover the RLD: 4,786,505 (expiry date 3/22/1999), 4,636,499 (expiry date 5/30/2005), 4,255,431 (expired on 6/22/98), 4,853,230 (expiry date 4/20/2007), 5,093,342 (2/2/2010), 5,599,794 (2/4/2014) and 5,629,305 (2/4/2014). The firm has filed a Paragraph IV certification against all of the patents except 4,255,431.

5. SUPPLEMENT(S)
N/A

6. PROPRIETARY NAME
Prilosec DRC®

7. NONPROPRIETARY NAME
Omeprazole

9. AMENDMENTS AND OTHER DATES:
Firm
Date filed: 3/17/98
Label amendment: 4/13/98
Bio amendment: 4/17/98
New correspondence: 5/28/98
New Correspondence: 5/29/98
Major amendment: 8/5/98
Bio Telephone amendment: 8/14/98
40 mg Strength amendment: 9/28/98
Facsimile amendment: 12/23/98
Facsimile amendment: 3/23/99
Telephone amendment: 4/16/99

FDA
Communication with ANDA filing date: 4/7/98
CMC Deficiency letter out: 7/20/98
Labeling comments out: 8/18/98
Bio sign off on approval: 8/24/98
Label deficiencies: 11/9/98
Chemistry deficiencies faxed: 12/11/98
Phone call by P. Rickman: 12/22/98
Bio Waiver for 40 mg: 1/11/99
Chemistry deficiencies faxed: 2/22/99
Phone call by Chemist: 4/15/99

10. PHARMACOLOGICAL CATEGORY
Gastric acid pump inhibitor

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)
DMF [redacted]

13. DOSAGE FORM
Delayed-release capsule

14. POTENCY
10 mg, 20 mg & 40 mg

15. CHEMICAL NAME AND STRUCTURE
5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1*H*-benzimidazole

16. RECORDS AND REPORTS
Method validation results are acceptable.
DMF is deficient.
Bio refused to grant waiver on the 40 mg strength; Bio deficieny letter is faxed to the firm on 4/9/99. The 40 mg strength requires a bio study.

17. COMMENTS
Major amendment will be requested.

18. CONCLUSIONS AND RECOMMENDATIONS
ANDA will require another DMF review and satisfactory bio review.

19. REVIEWER
Radhika Rajagopalan, Ph.D.

DATE COMPLETED
April 26, 1999

20. COMPONENTS AND COMPOSITION

Redacted 23

pages of

trade secret and/or

confidential

commercial

information

1. CHEMIST'S REVIEW #5

2. ANDA #75-347

3. NAME AND ADDRESS OF APPLICANT
Andrx Pharmaceuticals, Inc.
4001 S.W. 47th Avenue
Fort Lauderdale, FL 33314

4. LEGAL BASIS FOR ANDA SUBMISSION
Andrx Pharmaceuticals' proposed drug product, Omeprazole Delayed-release Capsules, 10 mg and 20 mg, is suitable for an Abbreviated New Drug Application on the basis that it is the same as the reference listed drug. The reference listed drug is Prilosec, Delayed-release capsule. The following patents cover the RLD: 4,786,505 (expiry date 3/22/1999), 4,636,499 (expiry date 5/30/2005), 4,255,431 (expired on 6/22/98), 4,853,230 (expiry date 4/20/2007), 5,093,342 (2/2/2010), 5,599,794 (2/4/2014) and 5,629,305 (2/4/2014). The firm has filed a Paragraph IV certification against all of the patents except 4,255,431.

5. SUPPLEMENT(S)
N/A

6. PROPRIETARY NAME
Prilosec DRC®

7. NONPROPRIETARY NAME
Omeprazole

9. AMENDMENTS AND OTHER DATES:
Firm
Date filed: 3/17/98
Label amendment: 4/13/98
Bio amendment: 4/17/98
New correspondence: 5/28/98
New Correspondence: 5/29/98
Major amendment: 8/5/98
Bio Telephone amendment: 8/14/98
40 mg Strength amendment: 9/28/98
Facsimile amendment: 12/23/98
Facsimile amendment: 3/23/99
Telephone amendment: 4/16/99
Correspondence: 6/14/99
Bio major amendment: 7/28/99
Telephone amendment: 8/6/99
Telephone amendment: 1/20/00

FDA
Communication with ANDA filing date: 4/7/98
CMC Deficiency letter out: 7/20/98
Labeling comments out: 8/18/98
Bio sign off on approval: 8/24/98
Label deficiencies: 11/9/98
Chemistry deficiencies faxed: 12/11/98
Phone call by P. Rickman: 12/22/98
Bio Waiver for 40 mg: 1/11/99
Chemistry deficiencies faxed: 2/22/99
Phone call by Chemist: 4/15/99
Chemistry deficiency fax: 5/15/99
Label deficiency fax: 5/18/99
Final label review: 7/12/99
Bio review on 40 mg dosage: 8/16/99
Phone call by PM and chemist: 12/23/99

10. PHARMACOLOGICAL CATEGORY
Gastric acid pump inhibitor

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)
DMF

13. DOSAGE FORM
Delayed-release capsule

14. POTENCY
10 mg, 20 mg & 40 mg

15. CHEMICAL NAME AND STRUCTURE
5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1*H*-benzimidazole

16. RECORDS AND REPORTS
Method validation results are acceptable.
DMF is adequate.
Bio refused to grant waiver on the 40 mg strength; Bio has completed review of the 40 mg strength and found the study acceptable.

17. COMMENTS
No outstanding chemistry deficiencies.

18. CONCLUSIONS AND RECOMMENDATIONS
Recommended for approval.

19. REVIEWER
Radhika Rajagopalan, Ph.D.

DATE COMPLETED
1/21/00

Redacted 21

pages of

trade secret and/or

confidential

commercial

information

1. CHEMIST'S REVIEW **#6**

2. ANDA **#75-347**

3. NAME AND ADDRESS OF APPLICANT
Andrx Pharmaceuticals, Inc.
4001 S.W. 47th Avenue
Fort Lauderdale, FL 33314

4. LEGAL BASIS FOR ANDA SUBMISSION
Andrx Pharmaceuticals proposed drug product, Omeprazole Delayed-release Capsules, 10 mg and 20 mg, is suitable for an Abbreviated New Drug Application on the basis that it is the same as the reference listed drug. The reference listed drug is Prilosec, Delayed-release capsule. The following patents cover the RLD: 4,786,505 (expiry date 3/22/1999), 4,636,499 (expiry date 5/30/2005), 4,255,431 (expired on 6/22/98), 4,853,230 (expiry date 4/20/2007), 5,093,342 (2/2/2010), 5,599,794 (2/4/2014) and 5,629,305 (2/4/2014). The firm has filed a Paragraph IV certification against all of the patents except 4,255,431. Paragraph IV certifications are provided on 3/26/01 for # 6150380, 6147103, 6166213 (expiry in 11/10/18) and 6191148 (10/09/18 expiry).

5. SUPPLEMENT(S)
N/A

6. PROPRIETARY NAME
Prilosec DRC®

7. NONPROPRIETARY NAME
Omeprazole

9. AMENDMENTS AND OTHER DATES:
Firm
Date filed: 3/17/98
Label amendment: 4/13/98
Bio amendment: 4/17/98
New correspondence: 5/28/98
New Correspondence: 5/29/98
Major amendment: 8/5/98
Bio Telephone amendment: 8/14/98
40 mg Strength amendment: 9/28/98
Facsimile amendment: 12/23/98
Facsimile amendment: 3/23/99
Telephone amendment: 4/16/99
Correspondence: 6/14/99
Bio major amendment: 7/28/99
Telephone amendment: 8/6/99
Telephone amendment: 1/20/00
Bioequivalence amendment: 12/20/00

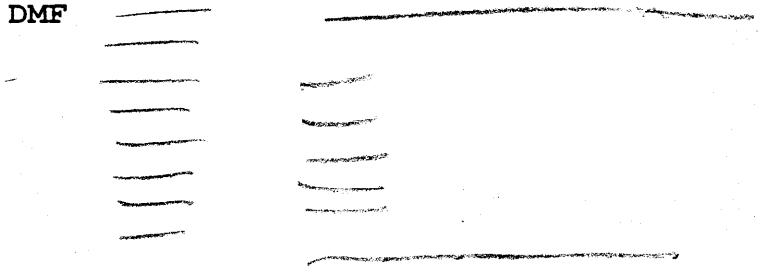
New Patent certifications: 3/20/01, 3/26/01

FDA
Communication with ANDA filing date: 4/7/98
CMC Deficiency letter out: 7/20/98
Labeling comments out: 8/18/98
Bio sign off on approval: 8/24/98
Label deficiencies: 11/9/98
Chemistry deficiencies faxed: 12/11/98
Phone call by P. Rickman: 12/22/98
Bio Waiver for 40 mg: 1/11/99
Chemistry deficiencies faxed: 2/22/99
Phone call by Chemist: 4/15/99
Chemistry deficiency fax: 5/15/99
Label deficiency fax: 5/18/99
Final label review: 7/12/99
Bio review on 40 mg dosage: 8/16/99
Phone call by PM and chemist: 12/23/99
Phone call by Doc room with regards to patent certification: 3/15/01
Chemistry amendment: 3/16/01 (new source of API)

10. PHARMACOLOGICAL CATEGORY
Gastric acid pump inhibitor

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)
DMF



13. DOSAGE FORM
Delayed-release capsule

14. POTENCY
10 mg, 20 mg & 40 mg

15. CHEMICAL NAME AND STRUCTURE
5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1*H*-benzimidazole

16. RECORDS AND REPORTS
DMF is inadequate (new API source).
Bio review of the 40 mg strength (new study) is pending.

17. COMMENTS
See item 38 for deficiencies.

18. CONCLUSIONS AND RECOMMENDATIONS
Minor amendment is requested.

19. REVIEWER — DATE COMPLETED
Radhika Rajagopalan, Ph.D. — 4/6/01

APPEARS THIS WAY
ON ORIGINAL

Redacted 27

pages of

trade secret and/or

confidential

commercial

information

1. CHEMIST'S REVIEW **#7**

2. ANDA **#75-347**

3. NAME AND ADDRESS OF APPLICANT
Andrx Pharmaceuticals, Inc.
4001 S.W. 47th Avenue
Fort Lauderdale, FL 33314

4. LEGAL BASIS FOR ANDA SUBMISSION
Andrx Pharmaceuticals proposed drug product, Omeprazole Delayed-release Capsules, 10 mg and 20 mg, is suitable for an Abbreviated New Drug Application on the basis that it is the same as the reference listed drug. The reference listed drug is Prilosec, Delayed-release capsule. The following patents cover the RLD: 4,786,505 (expiry date 3/22/1999), 4,636,499 (expiry date 5/30/2005), 4,255,431 (expired on 6/22/98), 4,853,230 (expiry date 4/20/2007), 5,093,342 (2/2/2010), 5,599,794 (2/4/2014) and 5,629,305 (2/4/2014). The firm has filed a Paragraph IV certification against all of the patents except 4,255,431. Paragraph IV certifications are provided on 3/26/01 for # 6150380, 6147103, 6166213 (expiry in 11/10/18) and 6191148 (10/09/18 expiry).

5. SUPPLEMENT(S)
N/A

6. PROPRIETARY NAME
Prilosec DRC®

7. NONPROPRIETARY NAME
Omeprazole

9. AMENDMENTS AND OTHER DATES:
Firm
Date filed: 3/17/98
Label amendment: 4/13/98
Bio amendment: 4/17/98
New correspondence: 5/28/98
New Correspondence: 5/29/98
Major amendment: 8/5/98
Bio Telephone amendment: 8/14/98
40 mg Strength amendment: 9/28/98
Facsimile amendment: 12/23/98
Facsimile amendment: 3/23/99
Telephone amendment: 4/16/99
Correspondence: 6/14/99
Bio major amendment: 7/28/99
Telephone amendment: 8/6/99
Telephone amendment: 1/20/00
Bioequivalence amendment: 12/20/00

New Patent certifications: 3/20/01, 3/26/01
Minor amendment: 7/30/01
Correspondence: 8/31/01
T-amendment to Chemistry: 9/11/01

FDA
Communication with ANDA filing date: 4/7/98
CMC Deficiency letter out: 7/20/98
Labeling comments out: 8/18/98
Bio sign off on approval: 8/24/98
Label deficiencies: 11/9/98
Chemistry deficiencies faxed: 12/11/98
Phone call by P. Rickman: 12/22/98
Bio Waiver for 40 mg: 1/11/99
Chemistry deficiencies faxed: 2/22/99
Phone call by Chemist: 4/15/99
Chemistry deficiency fax: 5/15/99
Label deficiency fax: 5/18/99
Final label review: 7/12/99
Bio review on 40 mg dosage: 8/16/99
Phone call by PM and chemist: 12/23/99
Phone call by Doc room with regards to patent certification: 3/15/01
Chemistry amendment: 3/16/01 (new source of API)
Minor amendment: 5/4/01
Phone call by chemist: 9/10/01

10. PHARMACOLOGICAL CATEGORY
Gastric acid pump inhibitor

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)
DMF

13. DOSAGE FORM
Delayed-release capsule

14. POTENCY
10 mg, 20 mg & 40 mg

15. CHEMICAL NAME AND STRUCTURE
5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1*H*-benzimidazole

16. RECORDS AND REPORTS
None

17. COMMENTS
ANDA was tentatively approved 5/23/00.
Subsequenlty, a new source [redacted], was added and a 40 mg strength batch was made. See comments in review for cycle #6.

18. CONCLUSIONS AND RECOMMENDATIONS
ANDA approval recommended.

19. REVIEWER | DATE COMPLETED
Radhika Rajagopalan, Ph.D. | 9/28/01

/S/ 10/4/01

APPEARS THIS WAY
ON ORIGINAL

Redacted 34

pages of

trade secret and/or

confidential

commercial

information

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-347

BIOEQUIVALENCE REVIEW

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA:75-347 APPLICANT: Andrx Pharmaceuticals, Inc.

DRUG PRODUCT: Omeprazole 40 mg delayed-release capsule

The Division of Bioequivalence has completed its review and has no further questions at this time.

We acknowledge that the following dissolution testing has been incorporated into your stability and quality control programs:

The dissolution testing should be conducted in [redacted] mg USP XXIII apparatus I (basket) at [redacted] The test product should meet the following specification:

NMT [redacted]

NLT [redacted]

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

/S/

Dale P. Conner, Pharm. D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA 75-347
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-650/ Reviewer

V:\FIRMSam\Andrx\ltrs&rev\75347S.899
Printed in final on / /

Endorsements: (Final with Dates)
HFD-655/ JLee 8/16/99
HFD-655/ Bio team Leader
HFD-650/ D. Conner 8/16/99

8/16/99

BIOEQUIVALENCY - ACCEPTABLE submission date:_____

1. **FASTING STUDY** (STF) 7/28/99 Strengths: 40 mg
Clinical: _____ ✓ **Outcome: AC**
Analytical: _____

5. **STUDY AMENDMENT** (STA) 8/6/99 Strengths: 40 mg
✓ **Outcome: AC**

Outcome Decisions: **AC** - Acceptable

WinBio Comments:
Fasted bio-study on 40 mg capsule is acceptable.

APPEARS THIS WAY
ON ORIGINAL

Omeprazole
10, 20 & 40 mg delayed-release capsules
NDA #75-347
Reviewer: J. Lee
75347S.301

Andrx Pharmaceuticals, Inc.
Fort Lauderdale, Florida
Submission date:
~~December 20, 2000~~ December 18, 2000 NCN
March 27, 2001

Review of an in-vivo Bioavailability Study and Dissolution Testing Data

This application received tentative approval on March 23, 2000. Acceptable bio-studies had been conducted on the 20 mg and 40 mg capsules.

The sponsor is now submitting an unsolicited bio-study on the 40 mg capsule *"in an effort to eliminate a stalling tactic used by innovator firms to delay generic competition for encapsulated pellet products. In the case of Tiazac, the approval of Andrx' ANDA was delayed by the NDA holder's labeling supplement for this form of administration* [sprinkling over applesauce] *a few months before the Andrx ANDA was eligible for final approval."*

The sponsor is concerned that Astra Zeneca will submit a similar labeling supplement to their NDA to permit administration by sprinkling over applesauce. Andrx is submitting a bio-study to show that their product is bioequivalent to Prilosec® when administered over applesauce.

Study Design:

The clinical study (#00210) was conducted at [redacted], under the supervision of [redacted]

Thirty healthy male volunteers between the ages of 18-50 years and within 10% of ideal body weight for his height and frame were enrolled in the study.

All selected volunteers were in good health as determined by a medical history, physical examination, clinical laboratory tests [hematology, serum chemistry and urinalysis], and EKG.

The study was designed as a randomized, open-label, two-way crossover study with a 7 day washout period between dosings. Treatments consisted of a single 40 mg dose of the following:

A. Omeprazole
40 mg delayed-release capsule, batch #640R001B
Andrx Pharmaceuticals, Inc..
expiry date: not given

B. Prilosec®
40 mg delayed-release capsule, batch #K5536
AstraZeneca, LP
expiry date: October, 2001

Thirty subjects were dosed according to the following schedule:

	Period I 09/10/00	Period II 09/17/00
sequence I	A	B
sequence II	B	A

sequence I - subj. # 1, 2, 4, 9, 11, 12, 13, 15, 16, 18, 20, 21, 25, 27, 28

sequence II - subj. #3*, 5, 6, 7, 8, 10, 14, 17, 19, 22, 23, 24, 26, 29*, 30*

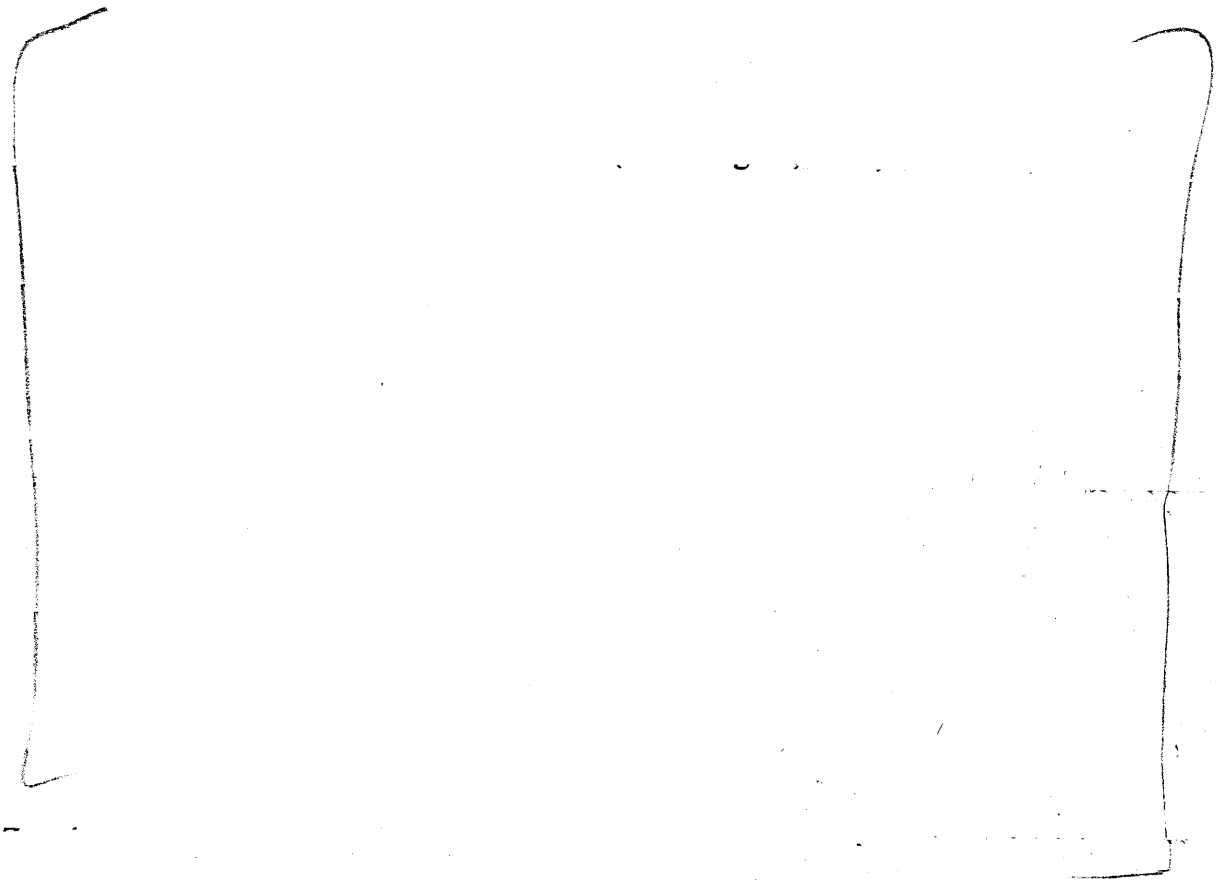
*dropouts – Subj #3 and 29 did not return for per II. Subj #30 was dropped from the study following per I dosing because during dosing, approximately 5 – 15% of the drug pellets fell off the applesauce medium; therefore, he did not receive a full dose.

After an overnight fast, subjects were given a 40 mg dose of omeprazole in applesauce [contents of one capsule were sprinkled onto one tablespoonful of applesauce]. Each subject swallowed the omeprazole/applesauce combination without chewing. Each dose was followed with 240 ml of water. Blood samples (10 ml) were drawn in
(pre-dose), 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 and 16 hours. All blood draws were taken within 2 minutes or 5% of the scheduled sampling time.

There was one adverse event reported (nausea, trt B) which was deemed possibly drug related. The event was moderate in severity and no therapy was required.

No significant deviations from protocol were reported.

Analytical: [Not for release under FOI]



Data Analysis:

The statistical analyses/report were generated by [redacted] Plasma data was analyzed by an analysis of variance procedure (SAS) determine statistically significant ($p<0.05$) differences between treatments, sequence of dosing, subjects within sequence and periods for the pharmacokinetic parameters and plasma level concentrations at each sampling time. The eliminate rate constant, Ke, for subject #25 (per II, ref.) could not be established due to the fluctuating concencentration values in the terminal phase; consequently, $t_{½}$ and AUC_{inf} could not be calculated for that subject. Of the original thirty subjects enrolled in the study, 27 completed the crossover; 27 datasets were analyzed.

Results:

No statistically significant differences were found in any of the major pharmacokinetic indices, neither on the original nor on the ln-transformed scale. No sequence effects were observed either. There was ≤4.6% difference between the test and reference formulations for plasma levels of omeprazole AUC_{0-t}, AUC_{inf} and C_{max}. The 90% shortest confidence intervals for omeprazole, using least squares means, are presented below:

90% CI

original scale	AUC_{0-t} (n=27)	[95.4; 110]
	AUC_{inf} (n=26)	[96.0; 111]
	C_{max} (n=27)	[83.1; 113]
ln-transformed scale	AUC_{0-t} (n=27)	[96.2; 111]
	AUC_{inf} (n=26)	[97.1; 113]
	C_{max} (n=27)	[83.1; 110]

Mean plasma level data and pharmacokinetic summary are attached.

In-vitro Dissolution:

The sponsor has conducted dissolution testing with test/reference bio-lots used in this study, using DBE's interim method. The dissolution summary is attached.

Potency and Content Uniformity:

The assay for content uniformity for 10 dosage units of the Andrx product was 101.7% of label claim; range = [redacted] (1.8% CV); for Prilosec®, the C.U. was 99.4% of label claim; range = [redacted] (2.9% CV). Assay for potency: 98.1% (Andrx); 100.6% (Prilosex®)

Batch Size:

The bio-batch size of Andrx' 40 mg omeprazole was stated to be [redacted] dosage units.

Comment:

1. This study employed the same batch of test product used in the original bio-study. A new batch of reference product was used in this study since the original RLD batch had expired.

Recommendation:

1. The bioequivalence study (with applesauce) conducted by [redacted] and [redacted] for Andrx Pharmaceuticals on its omeprazole 40 mg delayed-release capsule, batch #640R001, comparing it to Prilosec® 40 mg delayed-release capsule has been found acceptable by the Division of Bioequivalence. This study demonstrates that Andrx' omeprazole 40 mg delayed-release capsule is bioequivalent to Prilosec® 40 mg delayed-release capsule when adminstered with applesauce.

2. The in-vitro dissolution testing data is also acceptable. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in [redacted] specification:

NMT [redacted]
NLT [redacted]

/S/ 4/16/01

J. Lee
Division of Bioequivalence
Review Branch II

RD INITIALED SNERURKAR
FT INITIALED SNERURKAR

/S/ 4/25/2001

Concur: /S/ Date: 4/27/01

Dale Conner, Pharm. D.
Director, Division of Bioequivalence

JLee/jl/04-16-01

cc: NDA #75-347 (original, duplicate), HFD-630, HFD-655 (Lee, Patnaik), Drug File, Division File

APPEARS THIS WAY
ON ORIGINAL

USP XXIII Apparatus __I__ Basket __x__ Paddle ____ rpm

Medium:_____ _____Volume:_____ ml
Medium:_____ _____Volume:_____ ml

Number of Tabs/Caps Tested: 12

Reference Drug: Prilosec 40 mg capsule

Assay Methodology:_____

Results

Time (min)	Test Product Lot # 640R001			Reference Product Lot # K5536		
	Mean % Dissolved	Range	(CV)	Mean % Dissolved	Range	(CV)
2 hr (acid)*	1		(104)	3		(71.7)
10 min (buffer)	90		(3)	75		(3)
30	92		(2)	86		(3)
45	90		(2)	85		(3)

f_2=50.41

*percent dissolved was obtained by assaying the remaining pellets after subtracting from 100%.

APPEARS THIS WAY
ON ORIGINAL

OMEPRAZOLE 40 MG DR CAPSULE FASTING STUDY
ANDRX 00210
ARITHMETIC MEANS BY PRODUCT

---------- PRODUCT=A:TEST ----------

Variable	Label	N	Mean	Std Dev	CV
C1	0.00 HR	27	0.000	0.000	.
C2	0.50 HR	27	20.987	45.918	218.790
C3	1.00 HR	27	175.020	215.596	123.184
C4	1.50 HR	27	345.493	346.916	100.412
C5	2.00 HR	27	384.452	236.236	61.448
C6	2.50 HR	27	365.627	257.689	70.479
C7	3.00 HR	27	274.508	214.018	77.964
C8	3.50 HR	27	203.441	185.221	91.044
C9	4.00 HR	27	157.567	154.555	98.089
C10	5.00 HR	27	81.424	95.264	116.997
C11	6.00 HR	27	38.792	61.536	158.631
C12	7.00 HR	27	20.861	38.144	182.846
C13	8.00 HR	27	12.378	26.875	217.119
C14	9.00 HR	27	7.374	17.132	232.326
C15	10.0 HR	27	4.669	10.868	232.792
C16	11.0 HR	27	3.014	7.390	245.168
C17	12.0 HR	27	1.807	4.983	275.818
C18	13.0 HR	27	1.062	2.791	262.883
C19	14.0 HR	27	0.669	1.669	249.649
C20	16.0 HR	27	0.266	0.754	283.490

---------- PRODUCT=B:REFERENCE ----------

Variable	Label	N	Mean	Std Dev	CV
C1	0.00 HR	27	0.000	0.000	.
C2	0.50 HR	27	57.024	71.182	124.828
C3	1.00 HR	27	255.396	207.077	81.081
C4	1.50 HR	27	397.343	346.887	87.301
C5	2.00 HR	27	340.532	298.413	87.631
C6	2.50 HR	27	288.079	237.507	82.445
C7	3.00 HR	27	206.134	181.564	88.081
C8	3.50 HR	27	153.367	157.888	102.948
C9	4.00 HR	27	125.511	140.174	111.683
C10	5.00 HR	27	99.719	215.736	216.344
C11	6.00 HR	27	45.430	96.721	212.900
C12	7.00 HR	27	22.623	48.449	214.155
C13	8.00 HR	27	12.164	27.199	223.599
C14	9.00 HR	27	7.301	17.564	240.580
C15	10.0 HR	27	3.892	9.381	241.038
C16	11.0 HR	27	2.449	5.563	227.132
C17	12.0 HR	27	1.277	3.393	265.801
C18	13.0 HR	27	0.842	1.998	237.283
C19	14.0 HR	27	0.463	1.346	290.760
C20	16.0 HR	27	0.140	0.560	398.771

OMEPRAZOLE 40 MG DR CAPSULE FASTING STUDY
ANDRX 00210
SUMMARY OF STATISTICAL ANALYSIS OF NON-TRANSFORMED DATA

TITLE	TEST LEAST SQUARES MEAN	REFERENCE LEAST SQUARES MEAN	100* TEST/REFERENCE RATIO
AUCTLQC	1183.794	1150.201	103
AUCINF	1186.052	1144.274	104
CMAX	563.1667	573.3333	98.2
TMAX	2.175000	1.920833	113
KELM	0.768753	0.818289	93.9
THALF	1.046119	0.957474	109

TITLE	90% CI	POWER OF ANOVA	P VALUE
AUCTLQC	(95.4; 110)	0.99047	0.5110
AUCINF	(96.0; 111)	0.98744	0.4243
CMAX	(83.1; 113)	0.57516	0.8434
TMAX	(94.6; 132)	0.41318	0.2354
KELM	(84.6; 103)	0.93945	0.2775
THALF	(93.2; 125)	0.52436	0.3349

SUMMARY OF STATISTICAL ANALYSIS OF LOG-TRANSFORMED DATA

TITLE	TEST LEAST SQUARES MEAN LOG DATA	REFERENCE LEAST SQUARES MEAN LOG DATA	TEST GEOMETRIC MEAN	REFERENCE GEOMETRIC MEAN
AUCTLQC	6.882436	6.847661	974.999	941.676
AUCINF	6.884840	6.840546	977.345	934.999
CMAX	6.181614	6.228263	483.772	506.874

TITLE	100* RATIO OF GEOMETRIC MEANS	90% CI ON LOG TRANSFORMED DATA	POWER OF ANOVA FOR LOG TRANSFORMED DATA	P VALUE
AUCTLQC	104	(96.2; 111)	0.99226	0.4256
AUCINF	105	(97.1; 113)	0.99187	0.3135
CMAX	95.4	(83.1; 110)	0.65442	0.5710

GEOMETRIC MEANS BASED ON LEAST SQUARES MEANS
OF LOG TRANSFORMED VALUES.

CC: ANDA 75-347
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-650/ Reviewer

V:\FIRMSam\Andrx\ltrs&rev\75347S.301
Printed in final on / /

/S/ 4/25/01

Endorsements: (Typed with Dates)
HFD-655/ JLee /S/ 4/16/01
HFD-655/ Bio team Leader
HFD-650/ D. Conner /S/ 4/25/01

BIOEQUIVALENCY - ACCEPTABLE submission date: Dec ~~20,~~ 18 2000

1. **FASTING STUDY** (STF) Strengths: 40 mg
Clinical: ✓ **Outcome: AC**
Analytical:

5. **STUDY AMENDMENT** (STA)(Mar 27, 2001) Strengths: 40 mg
✓ **Outcome: AC**

Outcome Decisions: **AC** - Acceptable

WinBio Comments:
Bio-study (with applesauce) is acceptable.

APPEARS THIS WAY
ON ORIGINAL

(8)

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA #: 75-347 SPONSOR: Andrx Pharmaceuticals

DRUG AND DOSAGE FORM: Omeprazole delayed-release capsule

STRENGTH(S): 40 mg

TYPES OF STUDIES: bio-study administered w/applesauce

CLINICAL STUDY SITE(S): _____

ANALYTICAL SITE(S): _____

STUDY SUMMARY: study acceptable

DISSOLUTION: ok per DBE interim method

DSI INSPECTION STATUS

Inspection needed: YES / (NO)	Inspection status:	Inspection results:
First Generic no	Inspection requested: (date)	
New facility _____	Inspection completed: (date)	
For cause _____		
other _____		

PRIMARY REVIEWER: J. Lee BRANCH: II

INITIAL: /S/ DATE: 4/16/01

TEAM LEADER: SG Nerurkar BRANCH: II

INITIAL: /S/ DATE: 4/25/2001

DIRECTOR, DIVISION OF BIOEQUIVALENCE: DALE P. CONNER, Pharm. D.

INITIAL: /S/ DATE: 4/27/01

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

(7)

ANDA # : 75-347 SPONSOR : Andrx Pharmaceuticals

DRUG AND DOSAGE FORM : Omeprazole delayed-release capsule

STRENGTH(S) : 40 mg

TYPES OF STUDIES : fasted

CLINICAL STUDY SITE(S) : ———

ANALYTICAL SITE(S) : ———

STUDY SUMMARY : Meets 90% CI criteria

DISSOLUTION : ok per ——— interim method

DSI INSPECTION STATUS

Inspection needed: YES / (NO) - per Dale + J. Fan	Inspection status:	Inspection results: NOTE:
First Generic No ____ → Yes for 40mg only	Inspection requested: (date)	Andrx 20mg is the first to have P4.
New facility ____	Inspection completed: (date)	Clinical site: ———
For cause ____		Analytical: ———
Other ____		Both have good histories. No need for inspection for above. Jen.

PRIMARY REVIEWER : J. Lee BRANCH : II

INITIAL : /S/ _____ DATE : 8/16/99

TEAM LEADER : SG Nerurkar BRANCH : II

INITIAL : /S/ DATE : 8/16/1999

DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm. D.

INITIAL : /S/ _____ DATE : 8/16/99

Omeprazole
10, 20 & 40 mg delayed-release capsules
NDA #75-347
Reviewer: J. Lee
75347S.899

Andrx Pharmaceuticals, Inc.
Fort Lauderdale, Florida
Submission date:
July 28, 1999
August 6, 1999

Review of an in-vivo Bioavailability Study and Dissolution Testing Data

The sponsor has previously conducted acceptable fasted & fed bio-studies on their 20 mg capsule (rev. 8/26/98) and requested waiver of their 10 mg capsule based on formulation proportionality with the 20 mg capsule (common blend) and acceptable dissolution against the 10 mg RLD.

Subsequently, the sponsor amended their application with a 40 mg capsule and sought a waiver for an in-vivo study based on 21 CFR 320.22 (d)(2). This waiver request was originally granted, but later rescinded due to the discovery that the 40 mg Prilosec® was not formulation proportional to the 10 mg and 20 mg strength Prilosec®. A bio-study conducted by Astra/Merck also showed that the 40 mg Prilosec® was not bioequivalent to 2 x 20 mg Prilosec®.

The sponsor was then informed that an acceptable bio-study (fasted) on their 40 mg test product vs Prilosec® would be required for approval of this application (rev. 3/26/99). This submission contains that study.

Study Design:

The clinical study (#99145) was conducted at [redacted] under the supervision of [redacted].

Thirty healthy male volunteers between the ages of 18-50 years and within 10% of ideal body weight for his height and frame were enrolled in the study.

All selected volunteers were in good health as determined by a medical history, physical examination, clinical laboratory tests [hematology, serum chemistry and urinalysis], and EKG.

The study was designed as a randomized, open-label, two-way crossover study with a 7 day washout period between dosings. Treatments consisted of a single 40 mg dose of the following:

A. Omeprazole
40 mg delayed-release capsule, batch #640R001
Andrx Pharmaceuticals, Inc..
expiry date: not given

B. Prilosec®
40 mg delayed-release capsule, batch #H3531

Astra/Merck, Inc.
expiry date: October, 1999

Thirty subjects were dosed according to the following schedule:

	Period I 06/06/99	Period II 06/13/99
sequence I	A	B
sequence II	B	A

sequence I - subj. # 3, 4, 6, 7, 10, 11, 13, 16, 18, 21, 22, 23, 26, 28, 29

sequence II - subj. #1, 2, 5, 8, 9, 12, 14, 15, 17, 19, 20, 24, 25, 27, 30

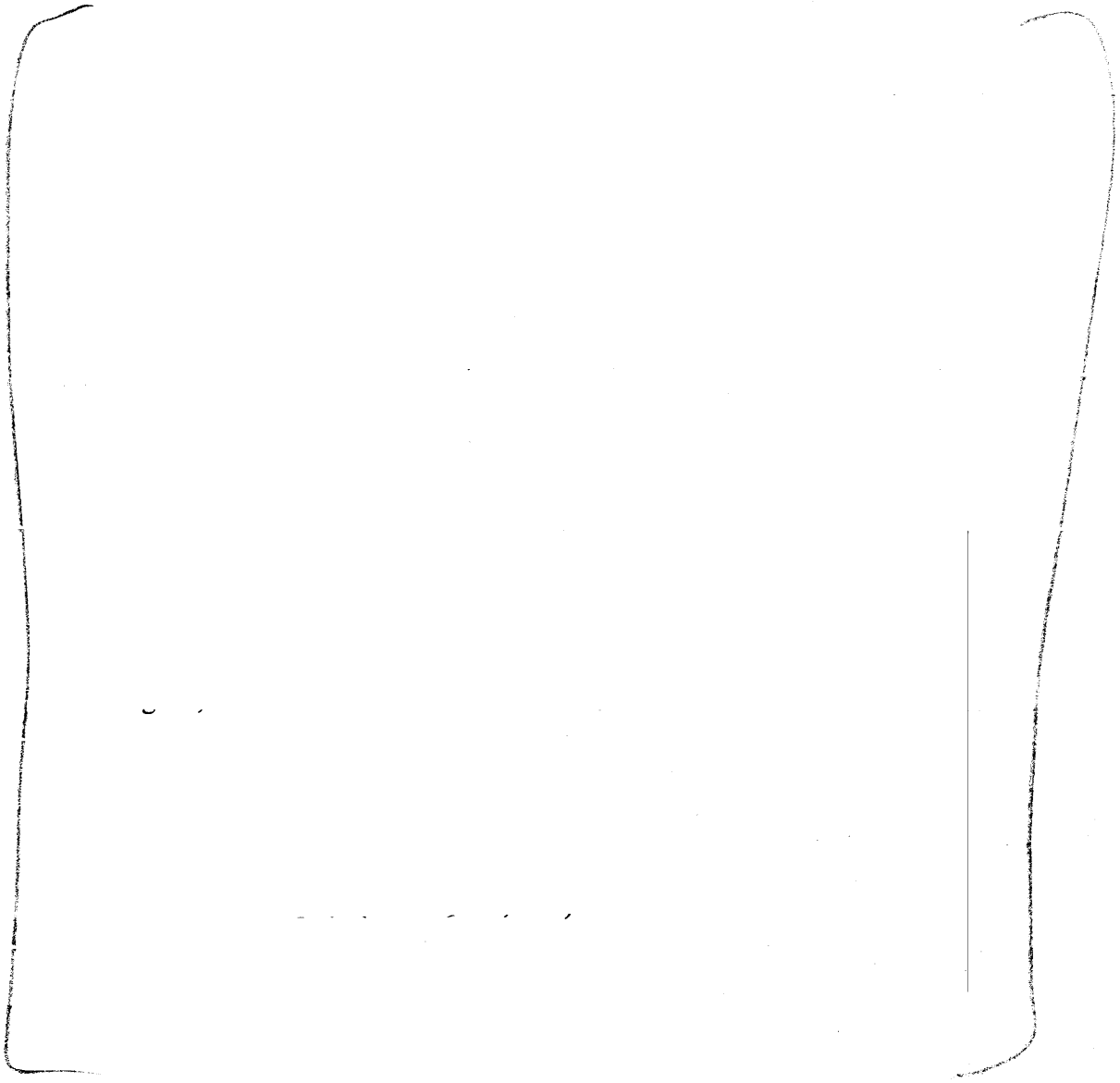
After an overnight fast, subjects were given a 40 mg dose of omeprazole with 240 ml of water. Fasting continued for 4 hours post-dose. Blood samples (10 ml) were drawn in [redacted] (pre-dose), 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 10 and 12 hours. All blood draws were taken within two minutes of the scheduled sampling time, except for two minor deviations. Those two exceptions were adjusted for in the PK calculations.

[redacted]

There were a total of 3 adverse events reported, only one of which (headache) was deemed possibly drug related. All events were mild/moderate in severity and no therapy was required in any of the adverse event instances.

No deviations from protocol were reported.

Analytical: [Not for release under FOI]



Data Analysis:

The statistical analyses/report were generated by [redacted] Plasma data was analyzed by an analysis of variance procedure (SAS) determine statistically significant ($p<0.05$) differences between treatments, sequence of dosing, subjects within sequence and periods for the pharmacokinetic parameters and plasma level concentrations at each sampling time. The eliminate rate constant, Ke, for subject #6 (ref.) could not be established due to the fluctuating concencentration values in the terminal phase; consequently, $t_{½}$ and AUC_{inf} could not be calculated for that subject. All thirty subjects enrolled in the study completed the crossover; thirty datasets were analyzed.

Results:

No statistically significant differences were found in any of the major pharmacokinetic indices, neither on the original nor on the ln-transformed scale. No sequence effects were observed either. There was ≤10% difference between the test and reference formulations for plasma levels of omeprazole AUC_{0-t}, AUC_{inf} and C_{max}. The 90% shortest confidence intervals for omeprazole, using least squares means, are presented below:

		90% CI
original scale	AUC_{0-t} (n=30)	[78.5; 106]
	AUC_{inf} (n=29)	[74.9; 106]
	C_{max} (n=30)	[78.7; 102]
ln-transformed scale	AUC_{0-t} (n=30)	[91.2; 106]
	AUC_{inf} (n=29)	[90.2; 105]
	C_{max} (n=30)	[84.6; 104]

Mean plasma level data and pharmacokinetic summary are attached.

In-vitro Dissolution:

The sponsor has conducted dissolution testing with test/reference bio-lots used in this study, using DBE's interim method. The dissolution summary is attached.

Content Uniformity:

The assay for content uniformity for 10 dosage units of the Andrx product was 103.4% of label claim; range = 100.5-106.0% (1.6% CV); for Prilosec®, the C.U. was 99.8% of label claim; range = 97.7-103.6% (2.0% CV).

Batch Size:

The bio-batch size of Andrx' 40 mg omeprazole was stated to be [redacted] dosage units.

Recommendation:

1. The bioequivalence study (fasted) conducted by [redacted] for Andrx Pharmaceuticals on its omeprazole 40 mg delayed-release capsule, batch #640R001, comparing it to Prilosec® 40 mg delayed-release capsule has been found acceptable by the Division of Bioequivalence.

2. The in-vitro dissolution testing data is also acceptable. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in [redacted]

XXIII apparatus I (basket) at — rpm. The test product should meet the following specification:

NMT —
NLT —

3. Bioequivalence requirements for the 40 mg omeprazole capsule have been met.

/S/ 8/16/99
J. Lee
Division of Bioequivalence
Review Branch II

RD INITIALED SNERURKAR
FT INITIALED SNERURKAR

/S/ 8/16/99

Concur: /S/ Date: 8/16/99

Dale Conner, Pharm. D.
Director, Division of Bioequivalence

JLee/jl/08-13-99

cc: NDA #75-347 (original, duplicate), HFD-630, HFD-655 (Lee, Patnaik), Drug File, Division File

APPEARS THIS WAY
ON ORIGINAL

USP XXIII Apparatus _I_ Basket _x_ Paddle ___ rpm ___

Medium: [redacted] Volume: [redacted] ml
Medium: [redacted] Volume: [redacted] ml

Number of Tabs/Caps Tested: 12

Reference Drug: Prilosec 40 mg capsule

Assay Methodology: [redacted]

Results

Time (min)	Test Product Lot # 640R001 Mean % Dissolved	Range	(CV)	Reference Product Lot # H3531 Mean % Dissolved	Range	(CV)
2 hr (acid)	1	[redacted]	(104)	5	[redacted]	(50)
10 min (buffer)	90	[redacted]	(3)	83	[redacted]	(3)
20	94	[redacted]	(2)	89	[redacted]	(3)
30	92	[redacted]	(2)	88	[redacted]	(3)
45	90	[redacted]	(2)	87	[redacted]	(3)

f_2=64.32

Mean Plasma Levels
(ng/ml)

OMEPRAZOLE 40 MG CAPSULE FASTING STUDY
ANDRX #99145
ARITHMETIC MEANS BY PRODUCT

PRODUCT=A:TEST

Variable	Label	N	Mean	Std Dev	CV
C1	0.00 HR	30	0.000	0.000	.
C2	0.50 HR	30	1.677	4.818	287.281
C3	1.00 HR	30	146.620	309.218	210.898
C4	1.50 HR	30	319.297	465.168	145.685
C5	2.00 HR	30	413.272	430.910	104.268
C6	2.50 HR	30	363.319	337.464	92.883
C7	3.00 HR	30	303.868	272.593	89.708
C8	3.50 HR	30	249.542	222.388	89.118
C9	4.00 HR	30	220.413	203.242	92.210
C10	5.00 HR	30	220.536	291.720	132.277
C11	6.00 HR	30	108.166	159.742	147.682
C12	7.00 HR	30	58.997	92.301	156.450
C13	8.00 HR	30	34.583	60.435	174.754
C14	10.0 HR	30	12.955	27.768	214.335
C15	12.0 HR	30	5.049	13.985	277.006

OMEPRAZOLE 40 MG CAPSULE FASTING STUDY
ANDRX #99145
ARITHMETIC MEANS BY PRODUCT

PRODUCT=B:REFERENCE

Variable	Label	N	Mean	Std Dev	CV
C1	0.00 HR	30	0.000	0.000	.
C2	0.50 HR	30	11.284	29.519	261.606
C3	1.00 HR	30	289.814	477.064	164.610
C4	1.50 HR	30	413.359	416.736	100.817
C5	2.00 HR	30	460.073	454.339	98.754
C6	2.50 HR	30	423.213	406.922	96.151
C7	3.00 HR	30	371.617	358.213	96.393
C8	3.50 HR	30	316.137	312.208	98.757
C9	4.00 HR	30	246.490	266.699	108.199
C10	5.00 HR	30	125.682	179.242	142.615
C11	6.00 HR	30	75.252	159.895	212.479
C12	7.00 HR	30	49.289	131.625	267.045
C13	8.00 HR	30	32.309	101.078	312.844
C14	10.0 HR	30	15.844	60.263	380.344
C15	12.0 HR	30	8.688	38.202	439.709

OMEPRAZOLE 40 MG CAPSULE FASTING STUDY
ANDRX #99145
SUMMARY OF STATISTICAL ANALYSIS OF NON-TRANSFORMED DATA

TITLE	TEST LEAST SQUARES MEAN	REFERENCE LEAST SQUARES MEAN	100* TEST/REFERENCE RATIO
AUCTLQC	1531.104	1661.879	92.1
AUCINF	1552.513	1716.912	90.4
CMAX	652.5667	720.2333	90.6
TMAX	2.766667	2.150000	129
KELM	0.756839	0.776697	97.4
THALF	1.061338	1.116260	95.1

TITLE	90% CI	POWER OF ANOVA	P VALUE
AUCTLQC	(78.5; 106)	0.66852	0.3358
AUCINF	(74.9; 106)	0.55376	0.3041
CMAX	(78.7; 102)	0.78987	0.1889
TMAX	(112; 146)	0.47579	0.0081
KELM	(87.3; 108)	0.89819	0.6714
THALF	(83.0; 107)	0.77875	0.4921

SUMMARY OF STATISTICAL ANALYSIS OF LOG-TRANSFORMED DATA

TITLE	TEST LEAST SQUARES MEAN LOG DATA	REFERENCE LEAST SQUARES MEAN LOG DATA	TEST GEOMETRIC MEAN	REFERENCE GEOMETRIC MEAN
AUCTLQC	7.054838	7.073946	1158.45	1180.80
AUCINF	7.067777	7.095086	1173.54	1206.03
CMAX	6.308923	6.374084	549.45	586.45

TITLE	100* RATIO OF GEOMETRIC MEANS	90% CI ON LOG TRANSFORMED DATA	POWER OF ANOVA FOR LOG TRANSFORMED DATA	P VALUE
AUCTLQC	98.1	(91.2; 106)	0.99256	0.6607
AUCINF	97.3	(90.2; 105)	0.98993	0.5422
CMAX	93.7	(84.6; 104)	0.89585	0.2863

GEOMETRIC MEANS BASED ON LEAST SQUARES MEANS
OF LOG TRANSFORMED VALUES.

RMSE

LAUCT	0.16681020
LAUCINF	0.16833920
LCMAX	0.23216555

File after - 3.23.99

Omeprazole
10, 20 & 40 mg delayed-release capsules
ANDA #75-347
Reviewer: J. Lee
75347O.D98

MAR 26 1999

Andrx Pharmaceuticals, Inc.
Fort Lauderdale, Florida
Submission date:
December 23, 1998

4.

Addendum to a Review

The sponsor was previously granted a waiver (rev. 1/13/99) of in-vivo studies on their 40 mg capsule based on the fact that the sponsor had previously conducted acceptable fasted and fed bio-studies on their 20 mg capsule. Initiation of the bio-studies (1st dose) on the 20 mg T/R products preceded the approval of 40 mg Prilosec® (1/15/98) and the generic sponsor uses a ——— in the composition of their pellets.

Recently, it came to light that the brand product does not use a ——— for its 10, 20 & 40 mg products. The 10 mg and 20 mg products are formulation proportional, but the 40 mg product is not proportional to the 10 mg/20 mg products. Furthermore, the bio-study on the 40 mg product, conducted by Astra/Merck, showed that the 40 mg product was not bioequivalent to 2 X 20 mg product [there was a 23% difference in treatment means for C_{max}].

Comment:

1. The Division of Bioequivalence is rescinding the waiver for the 40 mg omeprazole delayed-release capsule for the reasons outlined above.

Recommendation:

1. From the bioequivalence perspective, the sponsor must conduct an acceptable bio-study between their 40 mg test product vs Prilosec® 40 mg delayed-release capsule under fasted conditions for approval of this application.

/S/ - 3/25/99
J. Lee
Division of Bioequivalence
Review Branch II

RD INITIALED SNERURKAR
FT INITIALED SNERURKAR

/S/ 3/25/1999

Concur: /S/ Date: 3/26/99

Dale Conner, Pharm. D.
Director, Division of Bioequivalence

JLee/jl/03-25-99

cc: NDA #75-347 (original, duplicate), HFD-630, HFD-655 (Lee, Patnaik), Drug File, Division File

BIOEQUIVALENCY DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA:75-347 APPLICANT:Andrx Pharmaceuticals, Inc.

DRUG PRODUCT: Omeprezole 10, 20 & 40 mg delayed release capsules

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified.

1. The Division of Bioequivalence has determined that you must conduct an acceptable bio-study under fasted conditions employing your 40 mg capsule vs Prilosec® 40 mg capsule in order to obtain approval for the 40 mg strength product.

   While your capsule strengths are formulation proportional, the Prilosec® capsule strengths are not. The 40 mg Prilosec® capsule has been shown to be not bioequivalent to 2 X 20 mg Prilosec®.

   Therefore we are requiring the bio-study on the 40 mg capsule.

Sincerely yours,

/S/

Dale P. Conner, Pharm.D.
Director Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

CC: ANDA 75-347
ANDA DUPLICATE
DIVISION FILE
BIO DRUG FILE
FIELD COPY

Endorsements:
HFD-655/ Lee /S/ 3/25/99
HFD-650/ Nerurkar /S/ 3/25/99
HFD-617/ Mahmud
HFD-650/ Conner /S/ 3/26/99

Printed in draft on \ \
Printed in final on \ \
V:\firmsam\Andrx\ltrs&rev\75347O.D98

BIOEQUIVALENCY - DEFICIENCIES

8. **OTHER** (OTH) Dec 23, 1998 Strengths: 40 mg
Outcome: **UN**

OUTCOME DECISIONS:
UN - Unacceptable (fatal flaw)
WINBIO COMMENTS:

Previous waiver of the 40 mg capsule has been rescinded. Sponsor must conduct fasted bio-study on the 40 mg capsule.

APPEARS THIS WAY
ON ORIGINAL

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA:75-347 APPLICANT: Andrx Pharmaceuticals, Inc.

DRUG PRODUCT: Omeprazole 40 mg delayed-release capsule

The Division of Bioequivalence has completed its review and has no further questions at this time.

The following dissolution testing will need to be incorporated into your stability and quality control programs:

The dissolution testing should be conducted in [redacted]

following specification:

NMT [redacted]
NLT [redacted]

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

/S/

Dale P. Conner, Pharm.D.
Director Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

Rajagopalan-e 4.1

Omeprazole
10, 20 & 40 mg delayed-release capsules
NDA #75-347
Reviewer: J. Lee
75347DIW.D98

Andrx Pharmaceuticals, Inc.
Fort Lauderdale, Florida
Submission date:
September 28, 1998
December 23, 1998

Review of a Request for Waiver

The sponsor has previously conducted acceptable fasted and fed bio-studies on their 20 mg capsule and received a waiver on their 10 mg capsule (Rev. 26 Aug 98; J. Lee). The sponsor is amending their application to include a 40 mg strength product and is requesting a waiver of in-vivo requirements on their 40 mg test product. The sponsor has submitted comparative dissolution data between their 40 mg test product vs Prilosec® 40 mg delayed-release capsule as well as a formulation comparison between their 10, 20 & 40 mg capsules.

Comment:

1. Initiation of the bio-studies (1st dose) on the 20 mg T/R products preceded the approval of 40 mg Prilosec® (1/15/98).

2. The sponsor uses a [redacted] in the composition of the pellets.

3. The sponsor acknowledges the dissolution recommendation (sponsor's in-house method) mentioned in the Aug 26, 1998 review of this application and will use it until such time as the USP issues an official method or the Division of Bioequivalence deems it appropriate to change the dissolution method.

Recommendation:

1. The dissolution testing conducted by Andrx Pharmaceuticals on its omeprazole 40 mg delayed-release capsule, batch #640R001, is acceptable.

2. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in [redacted] meet the following specification:

NMT [redacted]
NLT [redacted]

4. The Division of Bioequivalence finds that the information submitted by the sponsor demonstrates that omeprazole 40 mg delayed-release capsule falls under 21 CFR 320.22 (d)(2) of Bioavailability/Bioequivalence Regulations. The Division of Bioequivalence

recommends that the waiver of an in-vivo bioavailability study be granted. Andrx' omeprazole 40 mg delayed-release capsule is deemed bioequivalent to Prilosec® 40 mg delayed-release capsule manufactured by Astra/Merck, Inc.

/S/ 1/6/99

J. Lee
Division of Bioequivalence
Review Branch II

RD INITIALED SNERURKAR
FT INITIALED SNERURKAR

/S/ 1/11/1999

Concur: /S/ Date: 1/13/99

Dale Conner, Pharm. D.
Director, Division of Bioequivalence

JLee/jl/ 01-05-99

cc: NDA #75-347 (original, duplicate), HFD-630, HFD-655 (Lee, Patnaik), Drug File, Division File

APPEARS THIS WAY
ON ORIGINAL

Current DBE Interim Method

USP XXIII Apparatus _I_ Basket _x_ Paddle ____ rpm [redacted]

Medium: [redacted] Volume: [redacted] ml
Medium: [redacted] Volume: [redacted] ml

Number of Tabs/Caps Tested: 12

Reference Drug: Prilosec® 40 mg capsule

Assay Methodology: [redacted]

Results

Time	Test Product			Reference Product		
	Lot # 640R001			Lot # H3094 Exp. June, 1999		
	Mean % Dissolved	Range	(CV)	Mean % Dissolved	Range	(CV)
2 hr (acid) [residue]	1*	[redacted]	(2)	0*	[redacted]	(2)
10 min (buffer)	90	[redacted]	(3)	79	[redacted]	(2)
20	94	[redacted]	(2)	89	[redacted]	(2)
30	92	[redacted]	(2)	90	[redacted]	(2)
45	90	[redacted]	(2)	89	[redacted]	(2)

*calculated as difference between 100% of label claim minus assayed amount in residue.

APPEARS THIS WAY
ON ORIGINAL

Table 1 **Composition and dose proportionality of Omeprazole Delayed-release Capsules, 10 mg, 20 mg, and 40 mg**

Ingredient	%	mg/capsule		
		10 mg cap	20 mg cap	40 mg cap
Active Pellets — of capsule content				
Omeprazole, USP		10.000	20.000	40.000
Sodium Lauryl Sulfate, NF				
Disodium Phosphate, USP				
Lactose				
Povidone, USP				
Pellets — of Capsule Content				
Hydroxypropyl Methylcellulose Phthalate, NF				
Cetyl Alcohol, NF				
Talc, USP				

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA:75-347 APPLICANT: Andrx Pharmaceuticals, Inc.

DRUG PRODUCT: Omeprazole 40 mg delayed-release capsule

The Division of Bioequivalence has completed its review and has no further questions at this time.

The following dissolution testing will need to be incorporated into your stability and quality control programs:

The dissolution testing should be conducted in [redacted]

following specification:

NMT [redacted]
NLT [redacted]

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

/S/

Dale P. Conner, Pharm.D.
Director Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA 75-347
ANDA DUPLICATE
DIVISION FILE
HFD-650/ Nerurkar for BioSign Off List
HFD-655/ J. Lee /S/ 1/6/99
BIO DRUG FILE

AC 1/11/99

Printed in Final on /S/ 1/13/99
V:\[redacted]\FIRMSam\Andrx\ltrs&rev\75347DIW.D98

BIOEQUIVALENCY - ACCEPTABLE

5. **STUDY AMENDMENT** (STA) 12/23/98 Strengths: 10, 20, 40 mg _____
Outcome: AC

7. **DISSOLUTION WAIVER** (DIW) Strengths: 40 mg _____
Outcome: AC

OUTCOME DECISIONS:
AC - Acceptable **NC** - No Action

WINBIO COMMENTS:
Waiver for 40 mg capsule acceptable per 21 CFR 320.22 (d)(2). Firm acknowledges and accepts DBE interim dissolution method.

APPEARS THIS WAY
ON ORIGINAL

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-347 APPLICANT: Andrx Pharmaceuticals, Inc.

DRUG PRODUCT: Omeprazole 10 & 20 mg delayed-release capsules

The Division of Bioequivalence has completed its review and has no further questions at this time.

You may use your proposed dissolution method until such time as the USP issues an official method or DBE deems it appropriate to change the dissolution method.

Please incorporate the following into your stability and quality control programs:

The dissolution testing should be conducted in [redacted]. The test product should meet the following specifications:

Not more than [redacted] (Q) of the labeled amount of the drug in the capsule is dissolved in [redacted]

Not less than [redacted] (Q) of the labeled amount of the drug in the capsule is dissolved in [redacted]

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

/S/

Dale P. Conner, Pharm.D.
Director Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA 75-347
ANDA DUPLICATE
DIVISION FILE
HFD-650/ Nerurkar for BioSign Off List
HFD-655/ J. Lee /S/ 8/20/98 /S/ 8/24/98
BIO DRUG FILE

Printed in Final on
X:\NEW\FIRMSam\Andrx\ltrs&rev\75347SDIW.898

BIOEQUIVALENCY - ACCEPTABLE

1. **FASTING STUDY** (STF) Strengths: 10 & 20 mg
Clinical: [redacted] **Outcome: AC**
Analytical: [redacted]

2. **FOOD STUDY** (STP) Strengths: 10 & 20 mg
Clinical: same **Outcome: AC**
Analytical: same

5. **STUDY AMENDMENT** (STA) 4/17/98 Strengths: 10 & 20 mg
Outcome: AC

6. **STUDY AMENDMENT** (STA) 8/14/98 Strengths: 10 & 20 mg
Outcome: AC

7. **DISSOLUTION WAIVER** (DIW) 4/17/98 Strengths: 10 mg
Outcome: AC

OUTCOME DECISIONS:
AC - Acceptable **NC** - No Action

WINBIO COMMENTS:
Fasted & fed bio-studies are acceptable. Dissolution method proposed by sponsor will be adopted by DBE as the interim method for this drug product.

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA/AADA # 75-347 SPONSOR: Andrx Pharmaceuticals, Inc.
DRUG: Omeprazole
DOSAGE FORM: delayed-release capsule
STRENGTHS/(s): 10 & 20 mg
TYPE OF STUDY: Single ✓ Multiple _ Fasting _ Fed ✓
STUDY SITE: _____

STUDY SUMMARY: Fasted & Fed Studies meet 80-125 CI
WAIVER GRANTED FOR 10 mg DR-CAPSULE.

DISSOLUTION: OK per sponsor's proposed method -

PRIMARY REVIEWER: Jenny Lee BRANCH: II

INITIAL: /S/ DATE 8/20/98

TEAM LEADER: S. Nerurkar, Ph.D BRANCH: II

INITIAL: /S/ DATE 8/24/98

DIRECTOR, DIVISION OF BIOEQUIVALENCE: Dale Conner, Pharm.D

INITIAL: /S/ DATE 8/26/98

DIRECTOR, OFFICE OF GENERIC DRUGS:

INITIAL: _____ DATE _____

Omeprazole
10 & 20 mg delayed-release capsules
NDA #75-347
Reviewer: J. Lee
75347SDIW.898

Andrx Pharmaceuticals, Inc.
Fort Lauderdale, Florida
Submission date:
March 17, 1998
April 17, 1998
August 14, 1998

Review of Fasted and Fed in-vivo Bioavailability Studies, Dissolution Testing Data and a Request for Waiver

Objective:

To determine the relative bioavailability of 20 mg omeprazole delayed-release capsules after administration of single doses to healthy male subjects under both fasted and fed conditions.

Fasted Study

Study Design:

The clinical study (#97273) was conducted at [redacted], under the supervision of [redacted]

Thirty healthy male volunteers between the ages of 21-35 years and within 10% of ideal body weight for his height and frame were enrolled in the study.

All selected volunteers were in good health as determined by a medical history, physical examination, clinical laboratory tests [hematology, serum chemistry and urinalysis], and EKG.

Those with any of the following conditions were excluded:

History or presence of:

- chronic alcoholism or drug abuse
- major organ dysfunction
- malignancy, stroke, diabetes, cardiac, renal or liver disease
- conditions which might contraindicate or require caution be used in the administration of omeprazole
- any illness or medication requirement that would affect gastric pH

Rx and OTC medications were not allowed within 14 and 7 days, respectively, of the first drug administration and for the duration of the study. There was to be no alcohol or caffeine consumption for 48 hours prior to drug administration.

The study was designed as a randomized, open-label, two-way crossover study with a 7 day washout period between dosings. Treatments consisted of a single 20 mg dose of the following:

A. Omeprazole
20 mg delayed-release capsule, batch #620R001
Andrx Pharmaceuticals, Inc..
expiry date: not given

B. Prilosec®
20 mg delayed-release capsule, batch #D2678
Astra/Merck, Inc.
expiry date: January, 1998

Thirty subjects were dosed according to the following schedule:

	Period I 12/13/97	Period II 12/20/97
sequence I	A	B
sequence II	B	A

sequence I - subj. # 3, 4, 6, 7, 10, 11*, 13, 16, 18, 21, 22, 23, 26, 28, 29

sequence II - subj. #1, 2, 5, 8, 9, 12, 14, 15, 17, 19, 20, 24, 25, 27, 30

*Subject #11 did not report for period II dosing for undisclosed personal reason(s).

After an overnight fast, subjects were given a 20 mg dose of omeprazole with 240 ml of water. Fasting continued for 4 hours post-dose. Blood samples (10 ml) were drawn in [redacted] pre-dose), 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8 and 10 hours. All blood draws were taken within two minutes of the scheduled sampling time.

[redacted]

Two subjects reported experiencing a total of 4 adverse events, only one of which (nausea, mild) was deemed probably drug related. All events were mild/moderate in severity and no therapy was required in any of the adverse event instances. The adverse events summary is summarized on page 114.

No deviations from protocol were reported.

Redacted 1

pages of

trade secret and/or

confidential

commercial

information

Data Analysis:

The statistical analyses/report were generated by [redacted] Plasma data was analyzed by an analysis of variance procedure (SAS) determine statistically significant ($p<0.05$) differences between treatments, sequence of dosing, subjects within sequence and periods for the pharmacokinetic parameters and plasma level concentrations at each sampling time. The eliminate rate constant, Ke, for subject #4 (ref.) and subjects #3 & 13 (test) could not be established due to the fluctuating concencentration values in the terminal phase; consequently, $t_{½}$ and AUC_{inf} could not be calculated for those subjects. Of the original thirty subjects enrolled in the study, one did not complete the crossover; twenty-nine datasets were analyzed.

Results:

No statistically significant differences were found in any of the pharmacokinetic indices, neither on the original nor on the ln-transformed scale, except for AUCinf ($p=0.0471$). No sequence effects were observed for the major bioavailability parameters. There was 13% difference between the test and reference formulations for plasma levels of omeprazole AUC_{0-t} and AUC_{inf}. The Andrx product produced a 1% higher C_{max} than the Astra/Merck product. The 90% shortest confidence intervals for omeprazole, using least squares means, are presented below:

		90% CI
original scale	AUC_{0-t} (n=29)	[102; 124]
	AUC_{inf} (n=27)	[102; 124]
	C_{max} (n=29)	[87.7; 121]
ln-transformed scale	AUC_{0-t} (n=29)	[98.8; 113]
	AUC_{inf} (n=27)	[100; 115]
	C_{max} (n=29)	[83.9; 106]

Mean plasma level data and pharmacokinetic summary are attached.

Fed Study

Study Design:

The clinical and analytical facilities for this study were the same as that employed in the fasting study. The [redacted] Inclusion and exclusion criteria for subject selection were also the same.

The study (#97274) was a randomized three treatment, three period, six sequence crossover. Treatments consisted of the same two batches of test and reference products (used in the fasted study). A 7 day washout period separated periods I and II; a 14 day washout separated periods II and III.

Eighteen subjects were dosed according to the following regimen:

	period I 01/04/98	period II 01/11/98	period III 01/25/98
sequence I	A	B	C
sequence II	A	C	B
sequence III	B	A	C
sequence IV	B	C	A
sequence V	C	A	B
sequence VI	C	B	A

sequence I - subj #1, 10*, 15*, 24*
sequence II - subj #4, 12, 14, 19
sequence III - subj #6, 9, 17, 20
sequence IV - subj #5*, 7, 16, 23*
sequence V - subj #3, 8, 13, 22
sequence VI - subj #2, 11, 18, 21*

Treatment A: 1 x 20 mg omeprazole capsule (Andrx) following an overnight fast
Treatment B: 1 x 20 mg omeprazole capsule (Andrx) following a standard breakfast*
Treatment C: 1 x 20 mg Priloxec® capsule (Astra/Merck) following a standard breakfast*

*standard breakfast:
1 buttered English muffin
1 fried egg
1 slice of American cheese
1 slice of Canadian bacon
1 serving (2.45 oz) of hash brown potatoes
6 fl oz of orange juice
8 fl oz of whole milk

*Of the 24 subjects enrolled in the study, four subjects (#5, 10, 23, 24) dropped from the study before initial dosing and were not replaced. Subjects #15 and 21 did not return to complete phase III of the study for personal reasons. Eighteen subjects completed all phases of the study.

After an overnight fast, subjects on treatment B or C were served a standard breakfast 15 minutes before dosing. Fasting continued for 4 hours post dose. The sampling schedule followed that used in the fasted study except for an additional 12 hour sampling. All blood draws were taken within 2 minutes of their target times.

There were a total of 3 mild clinical complaints reported [headache, stomach ache], all of which were judged possibly/probably related to the study drug. [see summary, p. 001215].

Analytical:

Data Analysis and Results:

Means, standard deviations and CV%s were calculated for the PK indices. Subject #13 had only one sample with a quantifiable level (per III). His period III data was eliminated in the statistical anaylses. There were a large number of subjects for which AUC_{inf} could not be calculated due to the erratic elimination profiles for those subjects after dosing with the T/R products under fed conditions. AUC_{inf} was not used in the bioequivalence determination in this study. Areas under the curve and C_{max} showed no difference for T/R (fed). There was a 27% decrease in AUC and a 40% decrease in C_{max} from the effect of a high-fat meal observed for T(fed)/T(fasted); T_{max} increased by more than 2-fold. Labeling indicates that the drug product be taken before meals. The results are summarized in appended tables.

In-vitro Dissolution:

The sponsor has conducted dissolution testing with test/reference bio-lots used in this study, using the sponsor's dissolution method:

(acid stage) USP XXIII Apparatus I (basket) @ 100 rpm
900 ml 0.1N HCl @ 37°C
for 2 hours [analyze residue]

(buffer stage) USP XXIII Apparatus I (basket) @ 100 rpm
900 ml pH 6.8 phosphate buffer @ 37°C
sampling at 10, 20, 30 and 45 minutes

Content Uniformity:

The assay for content uniformity for 10 dosage units of the Andrx product was 99.9% of label claim; range = 96.5-104.0% (2.3% CV); for Prilosec®, the C.U. was 99.0% of label claim; range = 96.5-101.0% (1.6% CV).

Batch Size:

The executed batch record for the bio-batch of Andrx' 20 mg omeprazole shows a reconciled yield of [redacted] dosage units.

Waiver Request:

The sponsor has requested a waiver of in-vivo requirements for their 10 mg omeprazole capsule. A quantitative formulation comparison between the 10 mg and 20 mg capsule was submitted, and comparative dissolution testing results were provided between the company's 10 mg test product vs Prilosec® 10 mg capsule.

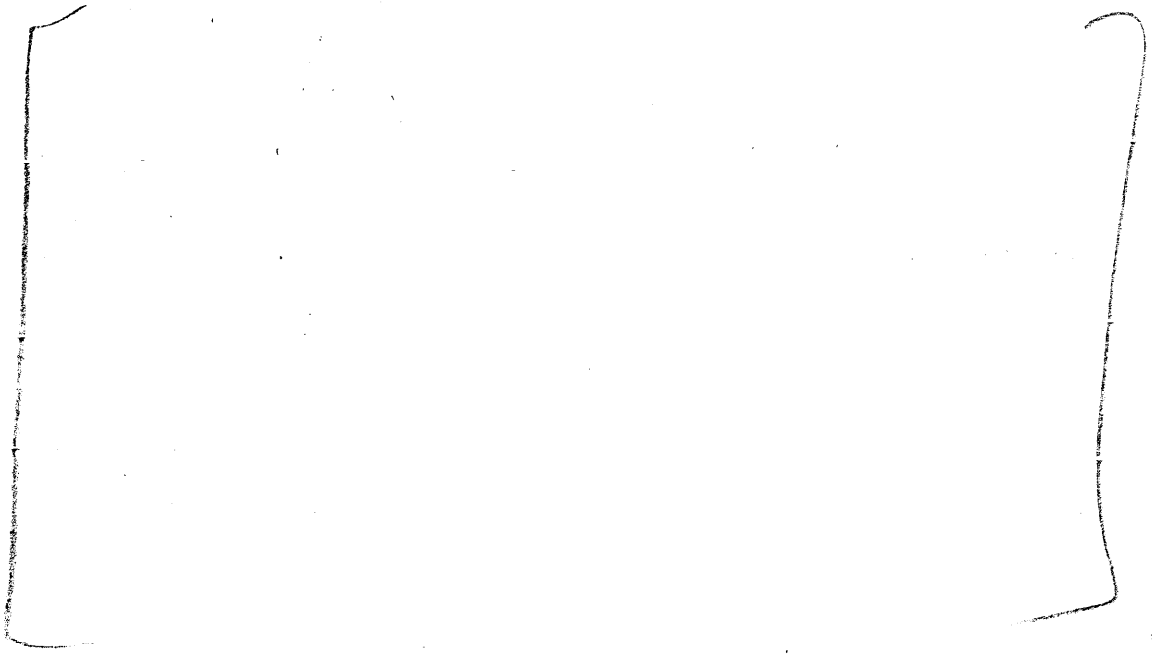
Comment:

1. The sponsor has conducted dissolution testing using their own method. There is currently no USP method available, but DBE has an interim method that it has been recommending and the sponsor was asked to conduct dissolution testing with the interim DBE method as follows:

Apparatus: USP paddle @ [redacted]
Media, volume: [redacted]
Sampling times: [redacted]

Tolerances: To be determined.

The results of both dissolution methods are attached.

2. 

.3 For the reasons listed above, the sponsor has proposed that their dissolution method or some modification be considered as the analytical method for the analysis of omeprazole delayed-release capsules.

4. The Division of Bioequivalence concurs that the sponsor's dissolution method is more suitable for this drug product and will recommend this method as the new interim dissolution method until such time as the USP issues an official method.

Recommendation:

1. The bioequivalence studies (fasted & fed) conducted by ' for Andrx Pharmaceuticals on its omeprazole 20 mg delayed-release capsule, batch #620R001, comparing it to Prilosec® 20 mg delayed-release capsule has been found acceptable by the Division of Bioequivalence. The study demonstrates that Andrx' omeprazole 20 mg delayed-release capsule is bioequivalent to the reference product, Prilosec® 20 mg delayed-release capsule manufactured by Astra/Merck, Inc.

2. The in-vitro dissolution testing data is also acceptable. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in XXIII apparatus I (basket) at ' he test product should meet the following specification:

NMT
NLT

3. The Division of Bioequivalence finds that the information submitted by sponsor demonstrates that omeprazole 10 mg delayed-release capsule falls under 21 CFR 320.22

(d)(2) of Bioavailability/Bioequivalence Regulations. The Division of Bioequivalence recommends that the waiver of an in-vivo bioavailability study be granted. Andrx Pharmaceuticals' 10 mg test product is deemed bioequivalent to Prilosec® 10 mg delayed-release capsule manufactured by Astra/Merck, Inc.

3. From the bioequivalence viewpoint the firm has met the requirements of in-vivo bioavailability and in-vitro dissolution testing and the application is acceptable.

/S/ 8/20/98

J. Lee
Division of Bioequivalence
Review Branch II

RD INITIALED SNERURKAR
FT INITIALED SNERURKAR

/S/ 8/25/1998

Concur: /S/ Date: 8/26/98

Dale Conner, Pharm. D.
Director, Division of Bioequivalence

JLee/jl/ 07-31-98

cc: NDA #75-347 (original, duplicate), HFD-630, HFD-655 (Lee, Patnaik), Drug File, Division File

APPEARS THIS WAY
ON ORIGINAL

DBE Interim Method

USP XXIII Apparatus II Basket _____ Paddle x rpm

Medium: _____ Volume: _____ ml
Medium: _____ Volume: _____ ml

Number of Tabs/Caps Tested: 12

Reference Drug: Prilosec 10 & 20 mg capsule

Assay Methodology: _____

Results 20 mg

Time (min)	Test Product Lot # 620R001			Reference Product Lot # D2678		
	Mean % Dissolved	Range	(CV)	Mean % Dissolved	Range	(CV)
2 hr (acid)	0		(0)	0		(0)
10 min (buffer)	37		(13)	83		(5)
20	47		(10)	86		(3)
30	49		(10)	85		(2)
45	49		(13)	83		(2)
60	49		(14)	80		(2)
65 (150 rpm)	74		(7)			( )
70 (150 rpm)	82		(4)			( )
			( )			( )
			( )			( )
			( )			( )

Results 10 mg

Time (min)	Test Product Lot # 610R002 Mean % Dissolved	Range	(CV)	Reference Product Lot # E2795 Mean % Dissolved	Range	(CV)
2 hr (acid)	0		(0)	0		(0)
10 min (buffer)	29		(14)	93		(3)
20	38		(14)	93		(3)
30	40		(15)	93		(3)
45	40		(14)	90		(3)
60	39		(14)	87		(3)
65 (150 rpm)	77		(3)			( )
70 (150 rpm)	77		(2)			( )
			( )			( )
			( )			( )
			( )			( )

APPEARS THIS WAY
ON ORIGINAL

Sponsor's Method

USP XXIII Apparatus _I_ Basket _x_ Paddle ____ rpm [redacted]

Medium: [redacted] Volume: [redacted] ml
Mediu[redacted] Volume: [redacted] ml

Number of Tabs/Caps Tested: 12

Reference Drug: Prilosec 10 & 20 mg capsule

Assay Methodology: [redacted]

Results

20 mg

Time	Test Product Lot # 620R001 Mean % Dissolved	Range	(CV)	Reference Product Lot # D2678 Mean % Dissolved	Range	(CV)
2 hr (acid) [residue] 6			(2)	7		(2)
10 min (buffer) 76			(16)	78		(4)
20	86		(3)	86		(3)
30	86		(2)	87		(3)
45	85		(2)	85		(3)

10 mg

	Lot # 610R002			Lot # E2795		
2 hr (acid) [residue] 6			(3)	5		(3)
10 min (buffer) 84			(5)	82		(4)
20	89		(4)	89		(4)
30	89		(4)	89		(4)
45	88		(4)	89		(5)

Mean Drug Levels and PK Summary - Fasted Study

Trt A (Andrx)

Variable	N	Mean	Std Dev	CV
Time (hr)		(ng/ml)		
0	29	0.242	1.304	538.5
0.5	29	4.687	15.135	322.9
1	29	60.796	81.841	134.6
1.5	29	138.749	168.315	121.3
2	29	147.728	158.513	107.3
2.5	29	140.315	165.604	118.0
3	29	133.306	182.666	137.0
3.5	29	116.601	188.976	162.1
4	29	99.029	170.191	171.9
5	29	69.271	131.645	190.0
6	29	33.826	82.782	244.7
7	29	19.866	56.962	286.7
8	29	13.893	43.339	311.9
10	29	6.424	22.550	351.0
AUCT	29	590.276	787.850	133.5
AUCINF	27	650.704	877.074	134.8
CMAX	29	259.428	195.705	75.4
TMAX	29	2.414	1.053	43.6
KEL	27	0.930	0.296	31.9
HL	27	0.875	0.473	54.1
LAUCT	29	5.943	0.840	14.1
LAUCINF	27	6.038	0.837	13.9
LCMAX	29	5.329	0.68192	12.8

Trt B (Prilosec)

Variable	N	Mean	Std Dev	CV
Time (hr)		(ng/ml)		
0	29	0	0	.
0.5	29	5.380	11.557	214.8
1	29	98.027	145.667	148.6
1.5	29	122.515	133.687	109.1
2	29	129.813	142.114	109.5
2.5	29	114.597	135.439	118.2
3	29	98.462	114.080	115.9
3.5	29	82.447	122.354	148.4
4	29	90.320	140.597	155.7
5	29	60.167	125.950	209.3
6	29	30.145	82.712	274.4
7	29	19.003	60.920	320.6
8	29	12.491	44.007	352.3
10	29	7.038	25.766	366.1
AUCT	29	522.655	626.794	119.9
AUCINF	28	571.143	724.596	126.9
CMAX	29	257.203	162.887	63.3
TMAX	29	2.224	1.222	54.9
KEL	28	0.999	0.356	35.6
HL	28	0.850	0.554	65.2
LAUCT	29	5.892	0.763	12.9
LAUCINF	28	5.962	0.769	12.9
LCMAX	29	5.386	0.568	10.5

Mean Drug Levels - Fed Study
ng/ml

Trt A (test-fast)

Time	N	Mean	Std Dev	CV
0	18	0.431	1.827	424.26
0.5	18	0.966	2.839	293.82
1	18	77.171	111.597	144.61
1.5	18	185.825	191.409	103.00
2	18	176.972	143.230	80.93
2.5	18	137.887	104.651	75.90
3	18	97.667	69.152	70.80
3.5	18	75.794	58.849	77.64
4	18	69.672	54.440	78.14
5	18	41.551	51.051	122.86
6	18	15.558	19.750	126.94
7	18	6.465	8.935	138.21
8	18	3.289	5.074	154.25
10	18	0.856	2.511	293.47
12	18	0	0	.

Trt B (test-fed)

Time	N	Mean	Std Dev	CV
0	17	0	0	.
0.5	17	3.083	10.971	355.87
1	17	0.000	0.000	.
1.5	17	0.000	0.000	.
2	17	0.799	2.271	284.34
2.5	17	7.201	20.430	283.73
3	17	4.382	8.498	193.91
3.5	17	11.690	25.904	221.59
4	17	27.156	32.720	120.49
5	17	107.512	96.394	89.66
6	17	94.312	71.053	75.34
7	17	63.867	89.715	140.47
8	17	35.762	46.481	129.97
10	17	8.265	18.347	221.99
12	17	7.137	19.997	280.18

Trt C (ref-fed)

Time	N	Mean	Std Dev	CV
0	18	0	0	.
0.5	18	2.114	4.426	209.38
1	18	3.971	8.651	217.89
1.5	18	4.664	10.089	216.29
2	18	9.177	19.276	210.06
2.5	18	12.186	21.072	172.93
3	18	21.373	33.882	158.52
3.5	18	34.437	39.748	115.42
4	18	42.179	50.819	120.48
5	18	106.983	67.614	63.20
6	18	78.211	82.889	105.98
7	18	43.215	57.564	133.20
8	18	28.199	49.694	176.23
10	18	8.077	15.522	192.18
12	18	5.345	13.055	244.25

Pharmacokinetic Summary - Fed Study

Trt A (test-fast)

Variable	N	Mean	Std Dev	CV	B/A
AUCT	18	492.556	319.882	64.94	0.735
CMAX	18	256.333	166.577	64.98	0.596
TMAX	18	2.333	1.272	54.51	2.294
KEL	18	0.965	0.310	32.11	
HL	18	0.791	0.254	32.12	
LAUCT	18	6.005	0.651	10.84	
LCMAX	18	5.355	0.639	11.93	

Trt B (test-fed)

Variable	N	Mean	Std Dev	CV	B/C
AUCT	17	362.235	257.761	71.16	1.005
CMAX	17	152.818	93.275	61.04	1.044
TMAX	17	5.353	1.183	22.10	1.031
KEL	8	0.813	0.247	30.43	
HL	8	0.938	0.333	35.56	
LAUCT	17	5.682	0.661	11.64	
LCMAX	17	4.874	0.564	11.57	

Trt C (ref-fed)

Variable	N	Mean	Std Dev	CV
AUCT	18	360.611	256.759	71.20
CMAX	18	146.344	68.026	46.48
TMAX	18	5.194	0.987	19.01
KEL	14	0.867	0.403	46.42
HL	14	1.049	0.648	61.81
LAUCT	18	5.712	0.599	10.49
LCMAX	18	4.893	0.443	9.05

Omeprazole Delayed-release Capsules, 10 and 20 mg		
Component	**10mg**	**20mg**
Active Pellets [redacted] of capsule content)		
[redacted]	[redacted]	[redacted]
Omeprazole, USP [redacted]	10.000	20.00
Sodium Lauryl sulfate, NF	[redacted]	[redacted]
Disodium Phosphate, USP	[redacted]	[redacted]
Lactose [redacted]	[redacted]	[redacted]
Povidone, USP [redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted] Pellets, [redacted] of Capsule Content		
Hydroxypropyl Methylcellulose Phthalate, NF [redacted]	[redacted]	[redacted]
Cetyl Alcohol, NF	[redacted]	[redacted]
Talc, USP	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-347 APPLICANT: Andrx Pharmaceuticals, Inc.

DRUG PRODUCT: Omeprazole 10 & 20 mg delayed-release capsules

The Division of Bioequivalence has completed its review and has no further questions at this time.

You may use your proposed dissolution method until such time as the USP issues an official method or DBE deems it appropriate to change the dissolution method.

Please incorporate the following into your stability and quality control programs:

The dissolution testing should be conducted in [redacted] 37°C using USP Apparatus I(basket) at [redacted] The test product should meet the following specifications:

Not more than [redacted] (Q) of the labeled amount of the drug in the capsule is dissolved in [redacted]

Not less than [redacted] (Q) of the labeled amount of the drug in the capsule is dissolved in [redacted]

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

/S/

Dale P. Conner, Pharm.D.
Director Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA 75-347
ANDA DUPLICATE
DIVISION FILE
HFD-650/ Nerurkar for BioSign Off List
HFD-655/ J. Lee /S/ 8/20/98
BIO DRUG FILE

/S/ 8/24/98 /S/ /S/ 8/24/98

Printed in Final on
X:\NEW\FIRMSam\Andrx\ltrs&rev\75347SDIW.898

BIOEQUIVALENCY - ACCEPTABLE

1. **FASTING STUDY** (STF) Strengths: 10 & 20 mg
Clinical: Outcome: **AC**
Analytical:

2. **FOOD STUDY** (STP) Strengths: 10 & 20 mg
Clinical: same Outcome: **AC**
Analytical: same

5. **STUDY AMENDMENT** (STA) 4/17/98 Strengths: 10 & 20 mg
Outcome: **AC**

6. **STUDY AMENDMENT** (STA) 8/14/98 Strengths: 10 & 20 mg
Outcome: **AC**

7. **DISSOLUTION WAIVER** (DIW) 4/17/98 Strengths: 10 mg
Outcome: **AC**

OUTCOME DECISIONS:
AC - Acceptable **NC** - No Action

WINBIO COMMENTS:
Fasted & fed bio-studies are acceptable. Dissolution method proposed by sponsor will be adopted by DBE as the interim method for this drug product.

APPEARS THIS WAY
ON ORIGINAL

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA/AADA # 75-347 SPONSOR: Andrx Pharmaceuticals, Inc.
DRUG: Omeprazole
DOSAGE FORM: delayed-release capsule
STRENGTHS/(s): 10 & 20 mg
TYPE OF STUDY: Single ✓ Multiple _ Fasting — Fed ✓
STUDY SITE: _____

STUDY SUMMARY: Fasted & Fed Studies meet 80-125 CI
WAIVER GRANTED FOR 10 mg DR-CAPSULE.

DISSOLUTION: OK per sponsor's proposed method -

PRIMARY REVIEWER: Jenny Lee BRANCH: II

INITIAL: /S/ DATE 8/20/98

TEAM LEADER: S. Nerurkar, Ph.D BRANCH: II

INITIAL: /S/ DATE 8/24/98

DIRECTOR, DIVISION OF BIOEQUIVALENCE: Dale Conner, Pharm.D

INITIAL: /S/ DATE 8/26/98

DIRECTOR, OFFICE OF GENERIC DRUGS:

INITIAL: _____ DATE _____

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-347 APPLICANT: Andrx Pharmaceuticals, Inc.

DRUG PRODUCT: Omeprazole 40 mg delayed-release capsule

The Division of Bioequivalence has completed its review of the bio-study administered with applesauce and has no further questions at this time.

We acknowledge that the following dissolution testing has been incorporated into your stability and quality control programs:

The dissolution testing should be conducted in [redacted]

USP Apparatus I (basket) at [redacted] The test product should meet the following specifications:

NMT [redacted] of the drug in the capsule is dissolved in [redacted]

NLT [redacted] of the drug in the capsule is dissolved in [redacted]

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

/S/

Dale P. Conner, Pharm. D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-347

ADMINISTRATIVE DOCUMENTS

DIVISION APROVAL SUMMARY

ANDA: 75-347 **DRUG PRODUCT:** Omeprazole Delayed-release Capsules, 10 mg, 20 mg and 40 mg

FIRM: Andrx Pharmaceuticals Inc.

DOSAGE: Capsules

STRENGTH: 10 mg, 20 mg and 40 mg

CGMP STATEMENT/EIR UPDATE STATUS:
CGMP: Certification provided on page 2459.
EIR: Acceptable as of 8/23/01.

BIO STUDIES/BIOEQUIVALENCE STATUS:
Acceptable 4/25/01.

METHODS VALIDATION:
Completed and found satisfactory by Atlanta labs.

STABILITY (conditions, containers and methods):
Bio batch was setup on stability in the proposed container/closure systems and data reported. The following are the firm's stability tests and specifications.

Stability Specs	
Test	Limits
Moisture	NMT — (capsule content only)
Assay (LC-label claim)	— of label claim
Dissolution	—:NMT — dissolved —: NLT —dissolved in —
Total Impurities	Individual known impurity: NMT —; Other unknown peaks: NMT — Total: NMT — (including
Physical appearance	10 mg- Light green cap/white — body, — capsule containing — 20 mg- Dark green cap/white — body, — capsule

Physical appearance	10 mg- Light green cap/white [redacted] body, [redacted] capsule containing [redacted] 20 mg- Dark green cap/white [redacted] body, [redacted] capsule containing [redacted] 40 mg- Dark green cap/light green [redacted] body, [redacted] capsule containing [redacted]

LABELING REVIEW STATUS:
Acceptable. See review dated 10/1/01

STERILIZATION VALIDATION (If Applicable):
NA.

BATCH SIZES:
Bio batch (identity #, drug substance source):
Two sources are indicated in the ANDA. They are: [redacted] and [redacted]

STABILITY BATCH (different from bio batch, manu. Site, process):
Stability batches are the same as bio batches.

PROPOSED PRODUCTION BATCH:
10 mg [redacted] capsules
20 mg [redacted] capsules
40 mg [redacted] capsules

COMMENTS:
None; approval recommended.

CHEMISTRY REVIEWER: Radhika Rajagopalan, Ph.D.
DATE: 9/28/01

/S/ 10/4/01
/S/ 10/4/01

APPEARS THIS WAY
ON ORIGINAL

orig Glen ltr.

TELEPHONE MEMO

To: Diane Servello and got voice mail
I was later able to reach Janet Von (Andrx Pharmaceuticals, Inc.)
954-581-7500

CC: ANDA 75-347 Omeprazole Delayed-release Capsules, 10 mg, 20 mg and 40 mg

From: Saundra T. Middleton

Date: March 15, 2001

Subject: Timely filed patents for omeprazole

The following patents for omeprazole were timely filed patents and you need to certify to them:

6150380 exp 11/10/18 drug substance

6147103 exp 10/9/18 drug substance

6166213 exp 10/9/18 drug substance

APPEARS THIS WAY
ON ORIGINAL

FROM THE DESK OF...

PROJECT MANAGER
CDER\FDA\OGD\DLPS
7500 STANDISH PLACE
ROCKVILLE MD 20855

301-827-5862
Fax: 301-594-1174

RECORD OF TELEPHONE CONVERSATION

I called Ms. D. Servello, the manager of regulatory affairs for Andrx Pharmaceuticals and requested her to amend stability and release specs. As recommended by the Division of Bioequivalence. She agreed to send a telephone amendment.

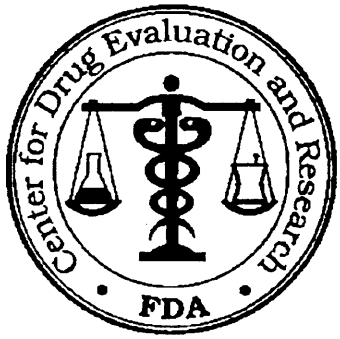
DATE 4/15/99
ANDA NUMBER 75-347
IND NUMBER
TELECON
INITIATED BY Jim Barlow MADE APPLICANT/ SPONSOR BY TELE. X FDA _ IN PERSON
PRODUCT NAME Omeprazole DR capsules
FIRM NAME Andrx
NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD Regulatory Affairs Manager
TELEPHONE NUMBER (954)327-4412
SIGNATURE /S/ 4/16/99

APPEARS THIS WAY
ON ORIGINAL

FACSIMILE AMENDMENT

ANDA 75-347

DEC 11 1998



OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

TO: APPLICANT: Andrx Pharmaceuticals, Inc. PHONE: 954-321-5229

ATTN: Jacqueline Davis FAX: 954-~~587-1054~~ 587-1054 ~~321~~

FROM: Kassandra Sherrod PROJECT MANAGER (301) 827–5849

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated March 17, 1998, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Omeprazole Delayed-release Capsules, 10 mg, 20 mg and 40 mg.

Reference is also made to your amendment(s) dated August 5 and September 28, 1998.

Attached are___ pages of minor deficiencies and/or comments that should be responded to within 30 calendar days from the date of this document. This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed. Your complete response should be (1) faxed directly to our document control room at 301- 827-4337, (2) mailed directly to the above address, and (3) the cover sheet should be clearly marked a FACSIMILE AMENDMENT.

Please note that if you are unable to provide a complete response within 30 calendar days, the file on this application will be closed as a MINOR AMENDMENT and you will be required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Accordingly, a response of greater than 30 days should be clearly marked MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. Facsimiles or incomplete responses received after 30 calendar days will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. You have been notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. Further if a major deficiency is cited in the bioequivalence review, the subsequent Not Approvable letter will request that the reply be declared a MAJOR AMENDMENT.

SPECIAL INSTRUCTIONS: Chemistry, bio and labeling comments attached KS 12/11/98

X:\new\ogdadmin\macros\faxfax.frm

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: **75-347** Date of Submission: **March 17, April 9, & September 28, 1998**

Applicant's Name: **Andrx Pharmaceuticals, Inc.**

Established Name: **Omeprazole Delayed-release Capsules, 10 mg, 20 mg & 40 mg**

Labeling Deficiencies:

1. CONTAINER (7s, 30s and 1000s)

   a. We encourage you to differentiate your product strengths with the use of boxing, contrasting colors or some other means.

   b. 10 mg & 20 mg

      Replace the "~~~ ..." statement with "Rx only". We refer you to "A GUIDANCE FOR INDUSTRY" entitled "Implementation of Section 126 of the Food and Drug Administration Modernization Act of 1997 - Elimination of Certain Labeling Requirements", was revised July 1998 and posted at Internet site http://www.fda.gov/cder/guidance/index.htm. Please note that Section IV, "Frequently Asked Questions" offers guidance on placement of the symbol on all labels and labeling.

   c. 40 mg

      Delete the "~~~" statement on the side panel.

   d. 7s - Include a statement that identifies this container size as a physician sample size.

   e. 30s - Include the following on the main panel:

      Unit-of-Use

f. 1000s - Replace the storage statement with the text "Dispense in a tight, light-resistant container. Protect from moisture."

2. INSERT (Submitted September 28, 1998)

a. GENERAL

i. We acknowledge that you have filed a Paragraph IV Patent Certification with regard to indication for "Treatment of H. Pylori associated with duodenal ulcer". However, we note that you have removed this information from your package insert labeling. Please retain this information (i.e., dual therapy with omeprazole/clarithromycin) in the insert labeling. Information regarding triple therapy (omeprazole/clarithromycin/ amoxicillin) for "Eradication of H. Pylori in patients with duodenal ulcer disease" should remain excluded from the insert labeling. Please refer to the enclosed annotated copy of the labeling of reference listed drug (Prilosec®; Astra Merck; Approved June 30, 1998; Revised June 1998). In addition, please revise the following:

ii. We ask you make a distinction between "subsection" and "sub-subsection" headings in terms of prominence throughout the text.

b. TITLE

See comment b under CONTAINER.

c. DESCRIPTION

i. Revise " [redacted] " to read "molecular formula".

ii. Revise " [redacted] to read "lactose monohydrate".

iii. You may delete " [redacted] and [redacted] form the listing of inactive ingredients.

iv. Last sentence- Revise to read:

The capsule shells and imprinting ink have...

d. CLINICAL PHARMACOLOGY (Clinical Studies, Gastric Ulcer) - Second table (*i.e.*, foreign study)

Revise to read "——" rather than "20 mg" in the center column.

e. HOW SUPPLIED

a. We encourage the relocation of "Rx only" to the TITLE section.

b. 40 mg

Include the reference to the sample size (7 capsules) and/or comment.

Please revise your labels and labeling, as instructed above, and submit 4 draft copies for a tentative approval or 12 final printed copies for a full approval of this application. If draft labeling is provided, please be advised that you will be required to submit 12 final printed copies of all labels and labeling at least 60 days prior to full approval of this application. In addition, you should be aware that color and other features (print size, prominence, etc) in final printed labeling could be found unacceptable and that further changes might be requested prior to approval.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

/S/

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Enclosure: Prilosec® labeling

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-347

CORRESPONDENCE

ANDA 75-347

APR 07 1998

Andrx Pharmaceuticals, Inc.
Attention: David A. Gardner
4001 S.W. 47th Avenue
Fort Lauderdale, FL 33314

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

NAME OF DRUG: Omeprazole Delayed-release Capsules, 10 mg and 20 mg

DATE OF APPLICATION: March 17, 1998

DATE (RECEIVED) ACCEPTABLE FOR FILING: March 17, 1998

You have filed a Paragraph IV patent certification, in accordance with 21 CFR 314.94(a)(12)(I)(A)(4) and Section 505(j)(2)(A)(vii)(IV) of the Act. Please be aware that you need to comply with the notice requirements, as outlined below. In order to facilitate review of this application, we suggest that you follow the outlined procedures below:

CONTENTS OF THE NOTICE

You must cite section 505(j)(2)(B)(ii) of the Act in the notice and should include, but not be limited to, the information as described in 21 CFR 314.95(c).

SENDING THE NOTICE

In accordance with 21 CFR 314.95(a):

- Send notice by U.S. registered or certified mail with return receipt requested to each of the following:

  1) Each owner of the patent or the representative designated by the owner to receive the notice;

2) The holder of the approved application under section 505(b) of the Act for the listed drug claimed by the patent and for which the applicant is seeking approval.

3) An applicant may rely on another form of documentation only if FDA has agreed to such documentation in advance.

DOCUMENTATION OF NOTIFICATION/RECEIPT OF NOTICE

You must submit an amendment to this application with the following:

- In accordance with 21 CFR 314.95(b), provide a statement certifying that the notice has been provided to each person identified under 314.95(a) and that notice met the content requirements under 314.95(c).

- In accordance with 21 CFR 314.95(e), provide documentation of receipt of notice by providing a copy of the return receipt or a letter acknowledging receipt by each person provided the notice.

- A designation on the exterior of the envelope and above the body of the cover letter should clearly state "PATENT AMENDMENT". This amendment should be submitted to your application as soon as documentation of receipt by the patent owner and patent holder is received.

DOCUMENTATION OF LITIGATION/SETTLEMENT OUTCOME

You are requested to submit an amendment to this application that is plainly marked on the cover sheet "PATENT AMENDMENT" with the following:

- If litigation occurs within the 45-day period as provided for in section 505(j)(4)(B)(iii) of the Act, we ask that you provide a copy of the pertinent notification.

- Although 21 CFR 314.95(f) states that the FDA will presume the notice to be complete and sufficient, we ask that if you are not sued within the 45-day period, that you provide a letter immediately after the 45 day period elapses, stating that no legal action was taken by each person provided notice.

- You must submit a copy of a final order or judgement from which no appeal may be taken (which might not be the one from the District Court), or a settlement agreement between the parties, whichever is applicable, or a licensing agreement between you and the patent holder, or any other relevant information. We ask that this information be submitted promptly to the application.

If you have further questions you may contact Peter Rickman, Chief, Regulatory Support Branch, at (301)827-5862.

We will correspond with you further after we have had the opportunity to review the application.

In addition, to be in compliance with 21 CFR 314.50(e)(2)(ii), you must provide four copies of the draft labels and labeling in the archival copy of the application. Please provide three additional copies draft package insert and container labels for the archival copy. In the future, please include four copies of the draft labels and labeling in **both** the archival and review copies of the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Kassandra Sherrod
Project Manager
(301) 827-5849

Sincerely yours,

/S/

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Andrx
PHARMACEUTICALS, INC.

April 16, 1999

Douglas L. Sporn, Director
Office of Generic Drugs, CDER, FDA
Attention: Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

FDA ORIG AMENDMENT
FA

RE: ANDA 75-347: Omeprazole Delayed-release Capsules, 10 mg, 20 mg and 40 mg

TELEPHONE AMENDMENT
SENT BY FAX TO 301-443-3839 – HARD COPY TO FOLLOW

Dear Mr. Sporn:

We refer to a telephone communication from Ms. Radhika Rajagopalan of your office on April 15, 1999. It was requested that we submit revised "Release" and "Stability" specifications reflecting the dissolution specifications described in our March 23, 1999 amendment. Accordingly, we have enclosed the following:

1. Stability/Release Specification Sheet for Omeprazole Delayed-release Capsules, 10 mg
2. Stability/Release Specification Sheet for Omeprazole Delayed-release Capsules, 20 mg
3. Stability/Release Specification Sheet for Omeprazole Delayed-release Capsules, 40 mg

Andrx Pharmaceuticals, Inc. certifies that a true copy of this amendment was sent to the Florida District Office as a Field Copy.

Should you have any questions concerning this submission, please contact the undersigned at (954) 327-4412 (telephone) or (954) 587-1054 (fax).

Sincerely,

Diane Servello
Director, Regulatory Affairs

RECEIVED
APR 20 1999
GENERIC DRUGS

4001 S.W. 47TH AVENUE, SUITE 201, FORT LAUDERDALE, FLORIDA 33314 • 954-581-7500 • FAX: 954-587-1054

5.1

Omeprazole DR Capsules
10 mg, 20 mg, and 40 mg
ANDA # 75-347
Reviewer : S. G. Nerurkar
V:\firmsam\Andrx\Ltrs&rev\75347OT.100

Andrx Pharmaceuticals Inc.
Fort Lauderdale , Fla
Submission Date :
January 20, 2000

Review of Correspondence

The three strengths of DR capsules in this ANDA were found to be acceptable by the Division of Bioequivalence (DBE)(See Ms. Lee's review dated 8-16-99 under V:\FIRMSam\Andrx\ltrs&rev\75347S.899). According to the review the following dissolution specifications were communicated to the firm.

NLT [redacted] of the drug in the capsule is dissolved in [redacted]
NLT [redacted] of the drug in the capsule is dissolved in [redacted]

Firm subsequently contacted the Division of Bioequivalence (DBE) via telephone to seek clarifications of the two dissolution related issues.

1st issue : The firm assumed that NLT [redacted] dissolution in buffer stage contains the NLT [redacted] dissolution in acid stage. In other words, if the acid stage dissolves [redacted] of the drug, then [redacted] issolution of the drug in the buffer stage (which makes [redacted] of drug dissolution in 2 stages) is acceptable.

Answer to the 1st issue : The firm's understanding is not correct. The percent dissolution is the buffer stage is independent of the percent dissolution in the acid stage. In other words, if the acid stage dissolves [redacted] of the drug, then [redacted] dissolution of the drug in the buffer stage (which makes [redacted] of the drug dissolution in 2 stages) is required.

2nd issue: Is it possible for DBE to change the dissolution specification in buffer stage from NLT [redacted] in [redacted] to NLT [redacted] in [redacted]

Answer to the 2nd issue: Based on the dissolution data in the DBE files, DBE will not change the dissolution specification. The time for dissolution will not be reduced from [redacted] minutes to [redacted]

DBE requested the firm to confirm in writing its understanding of the DBE answers. With this communication the firm has done so. **There is no need to communicate with the firm on this issue and for this submission.**

2/3/2000

/S/

S. G. Nerurkar, Ph.D.
Review Branch 2
Division of Bioequivalence

Concur : /S/ Date 3/17/00
Dale P. Conner
Director, Division of Bioequivalence

CC : ANDA 75-347 original, HFD-630, HFD 604, (OGD, Hare), HFD 22, (Hooton) HFC 130 (Jallen), HFD 655 (Nerurkar), Drug File

SGN/sgn/ 75347/2-2-2000

APPEARS THIS WAY
ON ORIGINAL

Andrx
PHARMACEUTICALS, INC.

VIA AIRBORNE EXPRESS

September 28, 1998

NDA ORIG AMENDMENT
N/AC

Douglas L. Sporn
Director, Office of Generic Drugs, HFD-600
CDER, Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: AMENDMENT: ANDA 75-347 (Omeprazole Delayed-release Capsules)

Dear Sir:

Please refer to Andrx's Abbreviated New Drug Application for Omeprazole Delayed-release Capsules, 10 mg & 20 mg, which was submitted on March 17, 1998.

In accordance with 21 CFR 314.96, we are amending this application to include a new 40 mg strength. Please note that all three strengths have a common formulation and are made by the same manufacturing process. This amendment contains revised labeling, *in vitro* dissolution data, a request for waiver of *in vivo* bioequivalence studies, and manufacturing and controls information for the 40 mg strength.

The amendment consists of 1 volume. **NOTE: THIS AMENDMENT CONTAINS AN ELECTRONIC SUBMISSION OF LABELING DATA** – the revised draft package insert is provided in WordPerfect v.6.1 and MS Word 97 format on two 3.5" diskettes. The data contained in the electronic submission is the same as in the hardcopy submission.

Andrx Pharmaceuticals, Inc. certifies that in accordance with 21 CFR 314.94(d)(5), a field copy of this amendment has been submitted to the Florida District Office concurrently with this submission. That field copy is a true copy of the chemistry, manufacturing, and controls technical sections contained in the archival and review copies of the application.

Please direct any questions regarding this submission to Jacqueline Davis, Regulatory Affairs Manager, at 954-321-5229 (Tel.) or 954-587-1054 (Fax.).

Sincerely,

RECEIVED
SEP 29 1998
GENERIC DRUGS

David A. Gardner
Vice President, Regulatory Affairs/QA/QC

4001 S.W. 47TH AVENUE, SUITE 201, FORT LAUDERDALE, FLORIDA 33314 • 954-581-7500 • FAX: 954-587-1054

Andrx
PHARMACEUTICALS INC.

NEW CORRESP.
NC to
Fax

VIA Facsimile

December 23, 1998

Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: ANDA #75-347: Omeprazole Delayed-Release Capsules, 10 mg, 20 mg, & 40 mg

FACSIMILE AMENDMENT

Dear Sir/Madam:

Andrx Pharmaceuticals is amending its abbreviated new drug application for Omeprazole Delayed-Release Capsules to provide the additional information requested by facsimile on December 11, 1998. This amendment provides a complete response to all the minor deficiencies and comments listed in the FDA's facsimile. It consists of one volume. An archival copy and two review copies (Chemistry and Bioequivalence) are provided.

In accordance with 21 CFR 314.96 (b), Andrx Pharmaceuticals certifies that a field copy of this amendment has been sent to the Florida District Office.

Should you have any questions concerning this submission, please contact the undersigned at (954) 321-5229 (tel.) or (954) 587-1054 (fax).

Sincerely,

Jacqueline Davis
Regulatory Affairs Manager

RECEIVED
DEC 24 1998

4001 S.W. 47th AVENUE, SUITE 201, FORT LAUDERDALE, FLORIDA 33314 • (954) 581-7500 • FAX (954) 587-1054

Andrx
PHARMACEUTICALS, INC.

VIA FACSIMILE

March 23, 1999

NEW CORRESP
NC to
Fax

Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: **ANDA #75-347: FACSIMILE AMENDMENT**
Omeprazole Delayed-release Capsules, 10 mg, 20 mg & 40 mg

Dear Sir/Madam:

Andrx Pharmaceuticals is amending its abbreviated new drug application for Omeprazole Delayed-release Capsules in response to the OGD's facsimile deficiencies dated February 22, 1999. This amendment provides a complete response to all the deficiencies and comments listed. It consists of one volume.

In accordance with 21 CFR 314.96(b), Andrx Pharmaceuticals certifies that a field copy of this amendment has been submitted to the Florida District Office.

Should you have any questions or comments concerning this submission, please contact the undersigned at (954) 321-5229 (telephone) or 954-587-1054 (facsimile).

Sincerely,

J. Davis

Jacqueline Davis
Regulatory Affairs Manager

RECEIVED
MAR 24 1999
GENERIC DRUGS

4001 S.W. 47TH AVENUE, SUITE 201, FORT LAUDERDALE, FLORIDA 33314 • 954-581-7500 • FAX: 954-587-1054

Andrx
PHARMACEUTICALS, INC.

July 28, 1999

ORIG AMENDMENT

AC

Douglas L. Sporn, Director
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: **ANDA #75-347: Omeprazole Delayed-release Capsules, 10 mg, 20 mg & 40 mg**

MAJOR AMENDMENT

Dear Mr. Sporn:

Andrx Pharmaceuticals is amending its abbreviated new drug application for Omeprazole Delayed-release Capsules in response to your letter dated May 18, 1999. This amendment provides a bioequivalence study for the 40 mg strength of this product. Please refer to our amendment dated June 14, 1999 for responses to the chemistry deficiencies cited in your May 18, 1999 letter.

In this regard, please find the following information:

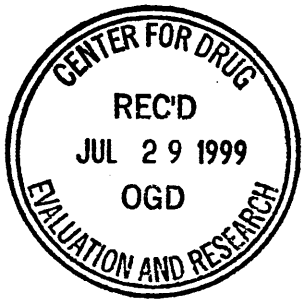
- Three volumes containing a study entitled "A randomized, two-way crossover, single-dose, open-label study to evaluate the relative bioavailability of a test delayed release capsule formulation of Omeprazole (40 mg), compared to an equivalent dose of a commercially available reference drug product (Prilocec®, Merck & Co., Inc.) in 30 fasted, healthy, male subjects" (Protocol No. 99145). A diskette containing the study data, along with a hard copy of the files contained on the diskette are included in Volume 1 of the Archival Copy.

Should you have any questions or comments concerning this submission, please contact the undersigned at (954) 327-4412 (telephone) or 954-587-1054 (facsimile).

Sincerely,

Diane Servello

Diane Servello
Director, Regulatory Affairs



4001 S.W. 47TH AVENUE, SUITE 201, FORT LAUDERDALE, FLORIDA 33314 • 954-581-7500 • FAX: 954-587-1054

Andrx
PHARMACEUTICALS, INC.

ORIG AMENDMENT
AC

June 14, 1999

Douglas L. Sporn, Director
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: **ANDA #75-347: Omeprazole Delayed-release Capsules, 10 mg, 20 mg & 40 mg**

MAJOR AMENDMENT/
REQUEST FOR RECLASSIFICATION TO MINOR AMENDMENT

Dear Mr. Sporn:

Andrx Pharmaceuticals is amending its abbreviated new drug application for Omeprazole Delayed-release Capsules in response to your letter dated May 18, 1999. This amendment provides a complete response to all the deficiencies and comments listed. This submission also includes a request to reclassify this major amendment to a minor amendment for the 10 mg and 20 mg strengths. The major deficiency identified in your May 18, 1999 letter concerns a newly communicated requirement for a bioequivalence study on the 40 mg strength only. Our bioequivalence study on the 40 mg strength is underway, and will be submitted upon completion. We are requesting that the tentative approval for the 10 mg and 20 mg strengths not be delayed pending the review of the new bioequivalence study on the 40 mg.

The basis for our request that this amendment be reclassified is as follows:

1. The May 18, 1999 major deficiency letter refers to a letter issued by the Division of Bioequivalence on April 9, 1999 notifying Andrx that an additional bioequivalence study is required on the 40 mg strength of this product. As discussed in the attached response, this bioequivalance study is ongoing and will be submitted upon completion.

2. The bioequivalence deficiency does not pertain to the 10 mg and 20 mg strengths of this product. Since each strength is considered to be a separate product, we are requesting that the tentative approval for the 10 mg and 20 mg strengths not be delayed pending the Agency's review of the 40 mg bioequivalence study.

3. Only one chemistry deficiency was cited in your May 18, 1999 letter. This was a DMF deficiency requiring a simple revision to the storage conditions in the labeling for the drug substance. From a CMC perspective, this response would clearly meet the criteria

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
JUN 15 1999
OGD

4001 S.W. 47TH AVENUE, SUITE 201, FORT LAUDERDALE, FLORIDA 33314 • 954-581-7500 • FAX: 954-587-1054

for a minor amendment, since it requires only the review of revised labeling for the drug substance.

In accordance with 21 CFR 314.96(b), Andrx Pharmaceuticals certifies that a field copy of this amendment has been submitted to the Florida District Office.

Should you have any questions or comments concerning this submission, please contact the undersigned at (954) 327-4412 (telephone) or 954-587-1054 (facsimile).

Sincerely,

Diane Servello
Director, Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

Andrx
PHARMACEUTICALS, INC.

March 22, 2000

Pat Beers-Block, Approvals Manager
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NEW CORRESP

RE: **ANDA #75-347: Omeprazole Delayed-release Capsules, 10 mg, 20 mg & 40 mg**

TELEPHONE AMENDMENT: CHEMISTRY MFG. & CONTROLS and PATENT INFORMATION

Dear Ms. Beers-Block:

Reference is made to our pending abbreviated new drug application for the above referenced drug product. Andrx Pharmaceuticals, Inc. ("Andrx") is amending its application to clarify the site of manufacture for the active drug substance. We are also reconfirming the Patent Certifications included in our original application.

1. We have enclosed a letter from [redacted] dated March 22, 2000. As mentioned in the attached letter, both lots of Omeprazole USP used in our biobatch were manufactured at [redacted] facility. The Certificate of Analysis that was included in our application for lot FX7246 mentioned [redacted] corporate address in [redacted] However, as indicated in the attached letter no [redacted] takes place at the [redacted] facility. Furthermore, the "F" prefix in the lot number identifies the [redacted] manufacturing site.

2. Our original application contained the following patent certifications:
   - Paragraph III: Patent #4,255,431 (expires on 04/05/01),
   - Paragraph IV: Patent #s 4,636,499 (expires 05/30/05), 4,853,230 (expires 04/20/07), 4,786,505 (expires 04/20/07), 5,093,342 (expires 02/02/10), 5,599,794 (expires 02/04/14) and 5,629,305 (expires 02/04/14).

   We acknowledge that because our application contains a paragraph III certification with respect to patent #4,255,431, expiring on April 5, 2001, this application can not receive final approval until this patent expires.

   As indicated in our Patent Amendment dated May 28, 1998 the holders of the patents listed in our paragraph IV certification filed an action for patent infringement against Andrx. That litigation is pending.

Andrx Pharmaceuticals, Inc. certifies that a true copy of this amendment was sent to the Florida District Office as a Field Copy.

Should you have any questions or comments concerning this submission, please contact the undersigned at (954) 327-4412 (telephone) or 954-587-1054 (facsimile).

Sincerely,

Diane Servello

Diane Servello
Director, Regulatory Affairs

CENTER FOR DRUG
REC'D
MAR 23 2000
OGD
EVALUATION AND RESEARCH

4001 S.W. 47TH AVENUE, SUITE 201, FORT LAUDERDALE, FLORIDA 33314 • 954-581-7500 • FAX: 954-587-1054

Andrx
PHARMACEUTICALS, INC.

NEW CORRESP

NC to FAX

January 20, 2000

Douglas L. Sporn, Director
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: **ANDA #75-347: Omeprazole Delayed-release Capsules, 10 mg, 20 mg & 40 mg**

TELEPHONE AMENDMENT

Dear Mr. Sporn:

Andrx Pharmaceuticals is amending it application to provide revised in-process and finished product specifications incorporating the dissolution specifications proposed by the Division of Bioequivalence on November 15, 1999.

This submission contains updated specifications for the enteric-coated pellets, the 10 mg, 20 mg, and 40 mg capsules. Three copies are provided – an archival copy, a chemistry review copy and a bioequivalence review copy.

Andrx Pharmaceuticals, Inc. certifies that a true copy of this amendment was sent to the Florida District Office as a Field Copy.

Should you have any questions or comments concerning this submission, please contact Jacqueline Davis, Regulatory Affairs Manager, at (954) 327-4412 (telephone) or 954-587-1054 (facsimile).

Sincerely,

Diane Servello
Director, Regulatory Affairs

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
JAN 28 2000
OGD

4001 S.W. 47TH AVENUE, SUITE 201, FORT LAUDERDALE, FLORIDA 33314 • 954-581-7500 • FAX: 954-587-1054

Andrx
PHARMACEUTICALS, INC.

ORIG AMENDMENT
N/AB

August 6, 1999

Douglas L. Sporn, Director
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: ANDA #75-347: Omeprazole Delayed-release Capsules, 10 mg, 20 mg, and 40 mg

TELEPHONE AMENDMENT

Dear Sir:

Reference is made to a telephone call from Jennifer Fan and Dr. Jenny Lee on August 5, 1999, requesting additional information for the test and reference products used in the 40 mg biostudy submitted on July 28, 1999. Accordingly, we are providing the following as a telephone amendment:

1. Comparative dissolution data for the 40 mg test and reference products (see attachment).

2. Potency and content uniformity results for the test and reference products:

	POTENCY, %	CONTENT UNIFORMITY, %
Test (Lot #640R001)	103.5	Avg.: 103.4 % RSD (n=10) : 1.6 Range: [redacted]
Reference (Lot #H3531)	99.8	Avg.: 100.2 % RSD (n=10) : 2.0 Range: [redacted]

3. Batch size of 40 mg test product (Lot #640R001) = [redacted] capsules).

Should you have additional questions, please contact the undersigned at (954) 327-4412 (Tel.) or (954) 587-1054 (Fax.).

Sincerely,

Diane Servello
Director of Regulatory Affairs

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
AUG 09 1999
OGD

4001 S.W. 47TH AVENUE, SUITE 201, FORT LAUDERDALE, FLORIDA 33314 • 954-581-7500 • FAX: 954-587-1054

Andrx
PHARMACEUTICALS, INC.

ANDA #: 75-347, Omeprazole Delayed-release Capsules, 10 mg, 20 mg and 40 mg

December 15, 2000

Gary Buehler,
Acting-Director, Office of Generic Drugs, HFD-600
CDER, Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NEW CORRESP

RE: General Correspondence

Dear Sir:

This letter is to inform you that the administrative offices of Andrx Pharmaceuticals, Inc. have relocated to a new address. Please direct all future correspondences pertaining to the above referenced ANDA to the following address and/or contact persons:

Andrx Pharmaceuticals, Inc.
4955 Orange Drive
Fort Lauderdale, Florida 33314

Diane Servello, *Director of Regulatory Affairs*
Telephone: (954) 585-1412

Janet Vaughn, *Manager of Regulatory Affairs*
Telephone: (954) 585-1665

Facsimile: (954) 587-1054

Please note that the manufacturing site for the drug product has not changed. The new address for the administrative offices is contiguous with the manufacturing site.

Should you have any questions or comments concerning these changes, please contact Janet Vaughn at the above telephone number.

Sincerely,

Janet Vaughn for
Diane Servello
Director, Regulatory Affairs

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
DEC 18 2000
OGD

Andrx
PHARMACEUTICALS, INC.

NDA CORRESP
NC

Return receipts via Fed Ex
No documentation of pre-authoriz.
Also no proof that 40 mg was consolidated w/ original suit.

June 28, 2000

Gary Buehler, Acting Director
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: **ANDA #75-347: Omeprazole Delayed-release Capsules, 10 mg, 20 mg & 40 mg**

LS
7/7/00

PATENT AMENDMENT

Dear Mr. Buehler:

We refer to the above referenced ANDA, which was tentatively approved on March 24, 2000. Upon a review of the paragraph IV patent notices for this application, it was noted that several patent notice-related documents were inadvertently not submitted to your office. The missing documents pertain to the 40 mg dosage strength of this product, which was submitted to this ANDA as an amendment on September 22, 1999. (The original ANDA submission, submitted on March 17, 1998 described only the 10 mg and 20 mg strengths.)

Due to an oversight, Andrx Pharmaceuticals, Inc. ("Andrx") did not submit documentation of receipt by the patent/NDA holder on June 3, 1999 of a second patent notice describing the new 40 mg strength product. A copy of documentation showing receipt of our second patient notice by Astra Pharmaceuticals LP ("Astra") is enclosed in Exhibit 1. In addition, a copy of cover page of the complaint initiated against Andrx by Astra on July 14, 1999 pertaining to the 40 mg strength was not submitted to your office. Please refer to Exhibit 2 for a copy of this document.

Please note that the court has consolidated Astra's second complaint against Andrx for the 40 mg strength with the first complaint pertaining to the 10 mg and 20 mg strengths. Therefore, one court decision will be made on all three dosage strengths. However, we acknowledge that for regulatory purposes, a separate 30 month period was started on June 3, 1999, the date the second patent notice was received by Astra.

Should you have any questions or comments concerning this submission, please contact the undersigned at (954) 327-4412 (telephone) or 954-587-1054 (facsimile).

Sincerely,

Diane Servello

Diane Servello
Director, Regulatory Affairs

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
JUN 29 2000
OGD

4001 S.W. 47TH AVENUE, SUITE 201, FORT LAUDERDALE, FLORIDA 33314 • 954-581-7500 • FAX: 954-587-1054

Andrx
PHARMACEUTICALS, INC.

ANDA 75-347
Omeprazole Delayed-release Capsules
10 mg, 20 mg and 40 mg

March 16, 2001

ORIG AMENDMENT
N/AC

Gary Buehler
Acting-Director, Office of Generic Drugs, HFD-600
CDER, Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: Amendment – Alternate Source of the Active Pharmaceutical Ingredient (API)

Dear Sir:

Please refer to Andrx Pharmaceuticals' abbreviated new drug application (ANDA) for Omeprazole Delayed-release Capsules, ANDA 75-347. Pursuant to 21 CFR 314.96 (a), Andrx is herewith submitting an amendment providing for an alternate source of the active pharmaceutical ingredient (API), Omeprazole, USP [redacted]. Please note that the current source of the [redacted], which was described in the tentatively approved ANDA, is not being withdrawn or substituted. This amendment is only intended to provide an additional source of the API.

The proposed [redacted] of Omeprazole, USP [redacted] is [redacted]. The API is manufactured at [redacted] manufacturing site located at the following address:

[redacted]

[redacted] manufactures the API consistent with the procedures and controls described in their Type II Drug Master File (DMF [redacted] which is currently on file with the FDA. A copy of a DMF authorization letter from [redacted] that authorizes Andrx Pharmaceuticals, Inc. to reference DMF [redacted] is provided in this amendment.

Omeprazole, USP (micronized) manufactured by [redacted] (Andrx lot 0002028) has been tested and shown to meet the same acceptance criteria as those of the omeprazole used in the original bioequivalence (ANDA) test batches. Andrx has also manufactured an exhibit batch of the 40 mg strength of the drug product using omeprazole manufactured by the proposed alternate source. The batch was manufactured in compliance with Policy and Procedure Guide 22-90, using the same manufacturing procedure and in process controls described in the ANDA, and packaged in 7, 30 and 1000 count bottles. Please note however, that the batch records for the active and enteric-coated pellets were slightly modified to accommodate a change in equipment size, that is, from a [redacted] to a [redacted]. A description of the modifications made and revised proposed commercial batch records that reflect the modifications are provided under Tab 6 of this amendment.

4955 ORANGE DRIVE, FORT LAUDERDALE, FLORIDA 33314 • 954 581-7500 • FAX: 954 587-1054

Accelerated (40°C/75% RH) stability data was generated on the exhibit batch (lot 640R003) and a comparative dissolution test performed versus the original 40 mg strength biobatch (lot 640R001). Please note that Andrx has adopted the dissolution procedure described in the *Pharmacopeial Forum* (PF) as the drug product is able to meet the PF criteria when this method is used. Revised release specifications and the revised standard test method are provided under Tab 8.

This amendment includes chemistry and manufacturing documentation that demonstrates that omeprazole, USP (micronized) from the proposed alternate source has no impact on the identity, strength, quality and purity of the final drug product. The exhibit batch, lot 640R003, meets the same release criteria as the original bioequivalence batches, has a similar *in-vitro* dissolution profile and remains stable for up to 3 months under accelerated stability conditions. A list of the chemistry and manufacturing documents included in this amendment is provided after the 356h form.

Andrx Pharmaceuticals, Inc. certifies that a true copy of this amendment was sent to the Florida District Office as a Field Copy.

Should you have any questions concerning this submission, please contact Janet Vaughn, Regulatory Affairs Manager at (954) 585-1665 (telephone) or (954) 587-1054 (fax).

Sincerely,

Diane Servello
Director of Regulatory Affairs

Andrx
PHARMACEUTICALS, INC.

NEW CORRESP

December 20, 2000

BIOAVAILABILITY

NC / Bio

Mr. Harvey Greenberg
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: ANDA #75-347 – Omeprazole Delay-release Capsules, 10 mg, 20 mg & 40 mg Bioequivalence Amendment

Dear Mr. Greenberg:

As per your telephone request of December 20, 2000 with Diane Servello, I have enclosed a signed original and copy of our 356h form for the above mentioned amendment.

Should you have any questions or comments concerning this submission, please contact the Diane Servello, Director of Regulatory Affairs, at (954) 585-1412 (telephone) or 954-587-1054 (facsimile).

Sincerely,

Jamie A. Dorgan

Jamie A. Dorgan
Associate, Regulatory Affairs

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
DEC 21 2000
OGD

4955 ORANGE DRIVE, FORT LAUDERDALE, FLORIDA 33314 · 954 581-7500 · FAX: 954 587-1054

Andrx
PHARMACEUTICALS, INC.

NDA ORIG AMENDMENT
N/AB

December 18, 2000

Gary Buehler, Acting Director
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: **ANDA #75-347: Omeprazole Delayed-release Capsules, 10 mg, 20 mg & 40 mg**

BIOEQUIVALENCE AMENDMENT

Dear Mr. Buehler:

Andrx Pharmaceuticals, Inc. ("Andrx") has conducted an additional bioequivalence study on our Omeprazole Delayed-release Capsules, 40 mg to compare the Andrx product to Prilosec® 40 mg Capsules when the capsule contents are sprinkled over applesauce. A copy of the final study report, consisting of **four (4) volumes**, is enclosed as follows:

> Study No. 00210: "A Randomized, Two-Way Crossover, Single-Dose, Open-Label Study to Evaluate the Relative Bioavailability of the Contents of a Test Delayed Release Capsules Formulation of Omeprazole (40 mg), on Applesauce, Compared to an Equivalent Dose of a Commerically Available Reference Drug Product (Prilosec®, Astra Zeneca LP) in 30 Fasted, Healthy Male Subjects"

This study was prepared in an effort to eliminate a stalling tactic used by innovator firms to delay generic competition for encapsulated pellet products. In the case of Tiazac, approval of Andrx' ANDA was delayed by the NDA holder's labeling supplement for this form of administration a few months before the Andrx ANDA was eligible for final approval.

With regard to this ANDA, we received tentative approval on March 23, 2000, and will be eligible for final approval upon the expiration of patent #4,255,431 (April 5, 2001), subject to a possible extension as a result of pediatric exclusivity. As we are concerned that Astra Zeneca will submit a similar labeling supplement to their NDA to permit administration by sprinkling over applesauce, Andrx is at this time submitting a bioequivalence study showing that the Andrx product is equivalent to Prilosec® when administered over applesauce.

Should you have any questions or comments concerning this submission, please contact the undersigned at (954) 585-1412 (telephone) or 954-587-1054 (facsimile).

Sincerely,

Diane Servello

Diane Servello
Director, Regulatory Affairs

Andrx
PHARMACEUTICALS, INC.

March 27, 2001

Gary Buehler, Acting Director
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT
N/AB

RE: **ANDA #75-347: Omeprazole Delayed-release Capsules, 10 mg, 20 mg & 40 mg**

BIOEQUIVALENCE TELEPHONE AMENDMENT

Dear Mr. Buehler:

Reference is made to our December 18, 2000 bioequivalence amendment to the above referenced ANDA. Reference is also made to a telephone communication between Jenny Lee and Nina Nwaba of the Division of Bioequivalence and Diane Servello of Andrx Pharmaceuticals, Inc. ("Andrx").

During the March 23 telephone communication it was requested that Andrx submit dissolution and potency data on the reference and test products used in Study No. 00210, which compared Andrx Omeprazole Delayed-release Capsules, 40 mg (lot #640R001) to Prilosec® 40 mg (lot #K5536) when administered by sprinkling over applesauce. Accordingly, please find the requested information attached.

Should you have any questions or comments concerning this submission, please contact the undersigned at (954) 585-1412 (telephone) or 954-587-1054 (facsimile).

Sincerely,

Diane Servello
Director, Regulatory Affairs

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
MAR 28 2001
OGD

4955 ORANGE DRIVE, FORT LAUDERDALE, FLORIDA 33314 • 954 581-7500 • FAX: 954 587-1054

Andrx
PHARMACEUTICALS, INC.

ANDA 75-347
Omeprazole Delayed-release Capsules

March 26, 2001

NEW CORRES
NC

Gary Buehler, Acting Director
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Re: Patent Certification

Dear Mr. Buehler:

Reference is made to a March 15, 2001 telephone communication between Saudra Middleton of the Office of Generic Drugs and Janet Vaughn of Andrx Pharmaceuticals, Inc. ("Andrx"). In that communication Andrx was requested to submit patent certifications for the following patents:

Patent Number	**Expiration Date**
6150380	11/10/18
6147103	10/09/18
6166213	10/09/18

In addition, we note that the following patent was listed on the March 19, 2001 Docket #95S-0117 *(Patent Term Extension and New Patents)*:

6191148	10/09/18

Andrx does not believe that these patent listings are appropriate, and therefore we are amending this application under protest to provide a paragraph IV patent certification for the four patents listed above. A letter providing the reasons for our belief that these patent listings are inappropriate will be sent under separate cover.

Should you have any questions concerning this submission, please contact the undersigned at (954) 585-1412 (telephone) or (954) 587-1054 (fax).

Sincerely,

Diane Servello
Director, Regulatory Affairs

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
MAR 26 2001
OGD

4955 ORANGE DRIVE, FORT LAUDERDALE, FLORIDA 33314 • 954 581-7500 • FAX: 954 587-1054

Andrx
PHARMACEUTICALS, INC.

ANDA #75-347
Omeprazole Delayed-release Capsules
10 mg, 20 mg, & 40 mg

ORIG AMENDMENT

N/AE

November 9, 2001

Gary Buehler,
Director, Office of Generic Drugs, HFD-600
CDER, Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: ANDA #75-347: Omeprazole Delayed-release Capsules, 10 mg, 20 mg & 40 mg

LABELING AMENDMENT

Dear Mr. Buehler:

Please refer to your October 31, 2001 facsimile requesting revisions to our package outsert for the above mentioned product (copy attached). The revision provides for the revision of the **PRECAUTIONS, Information for Patients** and the **DOSAGE AND ADMINISTRATION** sections of the package outsert to add information regarding the administration the enteric-coated pellets in applesauce for patients who may have difficult swallowing whole capsules.

Andrx Pharmaceuticals, Inc. has updated our labeling as requested in the facsimile. In this regard, we have enclosed the following:

1. Twelve (12) final printed package outserts.
2. A side-by-side comparison of our proposed labeling with our previous labeling, with all differences annotated and explained.

Should you have any questions concerning this submission, please contact the undersigned at (954) 585-1412 (telephone) or (954) 954-587-1054 (fax).

Sincerely,

Diane Servello
Director, Regulatory Affairs

CENTER FOR DRUG EVALUATION AND RESEARCH
NOV 0 9 2001
OGD

Enclosure(s)

Andrx
PHARMACEUTICALS, INC.

ANDA-75-347
Omeprazole Delayed-release Capsules, 10 mg, 20 mg and 40 mg

Via facsimile to (301) 443-3839

September 11, 2001

TELEPHONE AMENDMENT

M/Am

Gary Buehler, Director
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: TELEPHONE AMENDMENT

Dear Mr. Buehler:

Please refer to our ANDA for the above-mentioned drug product. Reference is also made to our July 30, 2001 minor amendment and to a September 10, 2001 telephone communication between Dr. Radika Rajagopalan of your office and Diane Servello of Andrx Pharmaceuticals, Inc.

This amendment includes stability data for the original ANDA test batches, lot numbers 610R002 (10 mg), 620R001 (20 mg), and 640R001 (40 mg) which were manufactured with omeprazole, USP from [redacted], the [redacted] Assay and related compounds test data at 43 months for the 10 mg and 20 mg capsules, and at 36 months for the 40 mg capsules, were obtained using the revised test method, STM #062, described in the July 30, 2001 minor amendment.

Andrx Pharmaceuticals, Inc. certifies that a Field Copy of this amendment was submitted to the Florida District Office. That field copy is a true copy of the information contained in this amendment.

Should you have any questions or comments concerning this amendment, please contact Janet Vaughn, Manager Regulatory Affairs, at (954) 585-1665 (Tel.) or 954-587-1054 (Fax.).

Sincerely,

Diane Servello

Diane Servello
Director Regulatory Affairs

CENTER FOR DRUG
SEP 14 2001

cc: Dr. Radika Rajagopolan
Chemistry Reviewer
Office of Generic Drugs

4955 ORANGE DRIVE, FORT LAUDERDALE, FLORIDA 33314 • 954 581-7500 • FAX: 954 587-1054

Andrx
PHARMACEUTICALS, INC.

9/11/01
Called Andrx.

ANDA-75-347
Omeprazole Delayed-release Capsules, 10 mg, 20 mg and 40 mg

July 30, 2001

Gary Buehler
Acting Director
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: MINOR AMENDMENT: CHEMISTRY

ORIG AMENDMENT

Dear Mr. Buehler:

Reference is made to your facsimile dated May 4, 2001 for the above referenced application (copy of facsimile attached). In accordance with 21 CFR 314.120, Andrx Pharmaceuticals, Inc. is submitting a minor amendment to this ANDA that provides a complete response to all the deficiencies listed in the facsimile.

A. Chemistry Deficiencies

1. **Please provide a revised components and composition statement, since the level of Povidone, USP, has been changed.**

Response

The revised components and composition statement, reflecting the change in the level of Povidone, USP, is provided under **Tab 1**.

2. **Please provide Certificates of Analysis for the inactive ingredients employed in the manufacture of batch 640R003.**

Response

Certificates of analysis for the lots of inactive ingredients employed in the manufacture of the exhibit batch, lot 640R003, are provided under **Tab 2**.

CENTER FOR DRUG EVALUATION AND RESEARCH
JUL 31 2001
OGD

3. **Please update specifications for inactive ingredients as per USP/NF 24.**

Response

The specifications for the inactive ingredients used in the exhibit batch are all in accordance with USP 24. The USP supplements are continuously monitored for changes and the specifications are updated as soon as changes are made to the monograph. A copy of the current specification for each excipient is provided under **Tab 2**. Please note that in accordance with our current practice, the specifications refer to the "current" version of the USP as the test method used rather than specifying the exact USP version.

4. **On page 159, [redacted] are missing. Please submit.**

Response

4955 ORANGE DRIVE, FORT LAUDERDALE, FLORIDA 33314 · 954 581-7500 · FAX: 954 587-1054

Redacted 3

pages of

trade secret and/or

confidential

commercial

information

Andrx
PHARMACEUTICALS, INC.

ANDA 75-347
MAJOR AMENDMENT

August 5, 1998

NDA ORIG AMENDMENT

N/AC

Douglas Sporn
Director, Office of Generic Drugs (HFD-600)
CDER, Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Dear Sir:

Please refer to Andrx's ANDA 75-347, for Omeprazole Delayed-release Capsules, 10 mg and 20 mg, and to the FDA's Not Approvable letter sent by facsimile on July 20, 1998.

This amendment provides a complete response to all the deficiencies listed in the Not Approvable letter. It consists of one volume, two copies of which are provided - an archival copy (blue binder) and chemistry review copy (red binder).

In accordance with 21 CFR 314.96(b), Andrx Pharmaceuticals certifies that a field copy of this amendment has been sent to the Florida District Office.

Please direct any questions regarding this submission to Jacqueline Davis, Regulatory Affairs Manager, by telephone at (954) 321-5229 or by facsimile at (924) 587-1054.

Sincerely,

David Gardner

David Gardner
Vice President, Regulatory Affairs/QA/QC

RECEIVED

AUG 0 7 1998

GENERIC DRUGS

4001 S.W. 47TH AVENUE, SUITE 201, FORT LAUDERDALE, FLORIDA 33314 • 954-581-7500 • FAX: 954-587-1054

Andrx
PHARMACEUTICALS, INC.

ANDA 75-347
PATENT AMENDMENT

May 28, 1998

NEW CORRESP
NC

Douglas L. Sporn, Director
Office of Generic Drugs (HFD-600)
CDER, Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Dear Mr. Sporn:

As required by 21 CFR 314.107(f)(2), Andrx Pharmaceuticals, Inc. is amending its Abbreviated New Drug Application for Omeprazole Delayed-release Capsules to provide notice of legal action against it for patent infringement:

RECEIVED
MAY 29 1998
GENERIC D...

(i) **ANDA No.:** 75-347

(ii) **Name of Applicant:** Andrx Pharmaceuticals, Inc.

(iii) **Established Name of Drug Product:**
Omeprazole Delayed-release Capsules, 10 mg and 20 mg

(iv) **Certification of Action for Patent Infringement:**
This certifies that an action for patent infringement (**Case No. 98-6521, CIV-GRAHAM**) has been filed by Astra Aktiebolag, Aktiebolaget Hassle, Astra Merck Enterprises, Inc., and Astra Merck, Inc. against Andrx Pharmaceuticals, Inc. alleging infringement of United States Patent No. 4,786,505 (the "505 patent"), Patent No. 4,853,230 (the "230 patent"), Patent No. 4,636,499 (the "499 patent"), Patent No. 5,599,794 (the "794 patent"), Patent No. 5,629,305 (the "305 patent"), Patent No. 5,093,342 (the "342 patent"), and Patent No. 4,255,431 (the "431 patent"). The complaint was filed in the United States District Court for the Southern District of Florida on May 21, 1998.

Please direct any questions regarding this submission to Jacqueline Davis, Regulatory Affairs Manager, by telephone at (954) 321-5229 or by fax at (954) 587-1054.

Sincerely,

David A. Gardner

David A. Gardner
Vice President, Regulatory Affairs/QA/QC

4001 S.W. 47TH AVENUE, SUITE 201, FORT LAUDERDALE, FLORIDA 33314 • 954-581-7500 • FAX: 954-587-1054

Andrx
PHARMACEUTICALS, INC.

ANDA 75-347
BIOEQUIVALENCE TELEPHONE AMENDMENT

AMENDMENT
N / AB

August 14, 1998

Douglas Sporn
Director, Office of Generic Drugs (HFD-600)
CDER, Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RECEIVED
AUG 17 1998
GENERIC DRUGS

Dear Mr. Sporn:

Andrx Pharmaceuticals is amending its Abbreviated New Drug Application for Omeprazole Delayed-release Capsules, 10 mg and 20 mg, to provide additional information as requested by Ms. Lizzie Sanchez and Dr. Jennie Lee by telephone on July 31, 1998. Specifically, we are providing additional dissolution data for the test and reference products using the dissolution test parameters recommended in that telephone call (see Attachment 1).

In addition, we are providing clarification of the lot numbering system used by Andrx for its finished products – The finished product lot numbers are designated *XXXAXXX(A),* where, using the 20 mg product (Lot #620R001) as an example, the first three digits represent the product code (620); the letter R indicates that this batch is a R&D/biobatch; and the last three digits are a sequential number assigned to each lot, starting with the first lot manufactured for each year (001). The final letter represents the packaging configuration e.g. 620R001A is the packaging lot number for the 7 capsules/bottle configuration and 620R001B is the lot number for the 30 capsules/bottle package size. A more detailed explanation can be found in Section XVIII (Control Numbers) of the original ANDA submission, a copy of which is provided as Attachment 2.

Should you have any questions or comments regarding this amendment please contact Ms. Jacqueline Davis, Regulatory Affairs Manager, Tel. (954) 321-5229/Fax. (954) 587-1054.

Sincerely yours,

David A. Gardner

David A. Gardner
Vice President, Regulatory Affairs/QA/QC

4001 S.W. 47TH AVENUE, SUITE 201, FORT LAUDERDALE, FLORIDA 33314 • 954-581-7500 • FAX: 954-587-1054

Andrx
PHARMACEUTICALS, INC.

NEW CORRESP
NC

ANDA 75-347
PATENT AMENDMENT

April 29, 1998

NAT 131 - 5/12/98

Douglas L. Sporn, Director
Office of Generic Drugs (HFD-600)
CDER, Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Dear Mr. Sporn:

Please refer to Andrx Pharmaceuticals' pending Abbreviated New Drug Application, ANDA 75-347, for Omeprazole Delayed-release Capsules, 10 mg and 20 mg.

In accordance with 21 CFR 314.95(b), Andrx Pharmaceuticals, Inc. certifies that notices of certification of invalidity or noninfringement of a patent have been provided by U.S. registered mail with return receipt requested to each person identified under 314.95(a) and that the notices met the content requirements under 314.95(c). The notices were sent on April 10, 1998, by James V. Costigan, patent counsel for Andrx Pharmaceuticals, Inc. In accordance with 21 CFR 314.95(e) a copy of the return receipt for each notice is provided in this amendment as documentation of receipt of notice.

This amendment consists of one volume. Two copies are provided - an archival copy (in a blue binder) and review copy (black binder). Please direct any questions regarding this submission to Jacqueline Davis, Regulatory Affairs Manager, by telephone at (954) 321-5229 or by fax at (924) 587-1054.

Sincerely,

David A. Gardner

David A. Gardner
Vice President, Regulatory Affairs/QA/QC

RECEIVED
MAY 0 1 1998
GENERIC DRUGS

4001 S.W. 47TH AVENUE, SUITE 201, FORT LAUDERDALE, FLORIDA 33314 • 954-581-7500 • FAX: 954-587-1054

BIOAVAILABILITY

Andrx
PHARMACEUTICALS, INC.

ORIG AMENDMENT
AB

ANDA 75-347
BIOEQUIVALENCE AMENDMENT

April 17, 1998

Douglas L. Sporn, Director
Office of Generic Drugs (HFD-600)
CDER, Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Dear Mr. Sporn:

Please refer to Andrx Pharmaceuticals' pending Abbreviated New Drug Application, ANDA 75-347, for Omeprazole Delayed-release Capsules, 10 mg and 20 mg.

Andrx Pharmaceuticals is amending this application to provide two replacement pages for an *in vivo* bioequivalence study report, Protocol No. 97273 (fasting study), submitted in the original application dated 3/17/98. We ask that pages 226 and 301 in volume 2 of the orginal application be replaced with the pages in this amendment. Two copies are provided - an archival copy (blue binder) and a bioequivalence review copy (orange binder).

Please direct any questions regarding this submission to Jacqueline Davis, Regulatory Affairs Manager, by telephone at (954) 321-5229 or by fax at (924) 587-1054.

Sincerely,

David A. Gardner

David A. Gardner
Vice President, Regulatory Affairs/QA/QC

RECEIVED
APR 20 1998
GENERIC DRUGS

4001 S.W. 47TH AVENUE, SUITE 201, FORT LAUDERDALE, FLORIDA 33314 • 954-581-7500 • FAX: 954-587-1054

Andrx
PHARMACEUTICALS, INC.

NEW CORRESP

April 13, 1998

Jerry Phillips, Director
Division of Labeling and Program Suppport
Office of Generic Drugs (HFD-600)
CDER, Food and Drug Administration
Metro Park North II
7500 Standish Place, Rm. 150
Rockville, MD 20855-2773

RE: **ANDA #75-347**

Dear Mr. Phillips:

Please refer to our Abbreviated New Drug Application for Omeprazole Delayed-release Capsules, 10 mg and 20 mg, which was submitted on March 17, 1998.

As requested in your April 7, 1998 correspondence we are providing three additional copies of the **draft container labels** submitted in our original application for the archival copy of the ANDA. Please note that four copies of our **revised package outsert labeling** were provided in **both** the archival and review copies of our 4/9/98 Labeling Amendment.

Should you have any questions or comments regarding this submission, please contact me by telephone at (954) 321-5229, or by fax at (954) 587-1054.

Sincerely,

Jacqueline Davis
Regulatory Affairs Manager

RECEIVED
APR 1 4 1998
GENERIC DRUGS

4001 S.W. 47TH AVENUE, SUITE 201, FORT LAUDERDALE, FLORIDA 33314 • 954-581-7500 • FAX: 954-587-1054

Andrx
PHARMACEUTICALS, INC.

April 9, 1998

NDA ORIG AMENDMENT
N /AF

Douglas L. Sporn, Director
Office of Generic Drugs
CDER, Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: **ANDA #75-347 Omeprazole Delayed-release Capsules, 10 mg & 20 mg**
LABELING AMENDMENT

Dear Mr. Sporn:

Please refer to our Abbreviated New Drug Application for Omeprazole Delayed-release Capsules, 10 mg and 20 mg, which was submitted on March 17, 1998.

Andrx Pharmaceuticals hereby amends this application to provide revised package outsert labeling. The proposed labeling has been revised to delete all references to the use of omeprazole in [redacted] as this use is under patent protection. As reflected in the revised labeling, Andrx's Omeprazole Delayed-release Capsules will not be marketed for this use. This amendment consists of one volume. Two copies are provided - an archival copy (blue binder) and a review copy (red binder).

Please direct any questions or comments regarding this submission to Jacqueline Davis, Regulatory Affairs Manager at (954) 321-5229.

Sincerely,

David A. Gardner

David A. Gardner
V.P., Regulatory Affairs, QA/QC

RECEIVED
APR 13 1998
GENERIC DRUGS

4001 S.W. 47TH AVENUE, SUITE 201, FORT LAUDERDALE, FLORIDA 33314 • 954-581-7500 • FAX: 954-587-1054

Andrx
PHARMACEUTICALS, INC.

March 17, 1998

Douglas L. Sporn, Director
Office of Generic Drugs
CDER, Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

505(j)(2)(a) OK
/S/ 1/2/98
/S/

RE: **Abbreviated New Drug Application**
OMEPRAZOLE DELAYED-RELEASE CAPSULES, 10 mg & 20 mg

Dear Mr. Sporn:

Pursuant to the requirements of Section 505(j) of the Federal Food, Drug and Cosmetic Act and 21 CFR §314.94, Andrx Pharmaceuticals, Inc. ("Andrx") is submitting an original Abbreviated New Drug Application ("ANDA") for approval to market Omeprazole Delayed-release Capsules, 10 mg and 20 mg.

This ANDA contains information to demonstrate that Andrx's Omeprazole Delayed-release Capsules are the same as the reference listed drug, Prilosec® (Omeprazole) Delayed-release Capsules, manufactured by Astra Merck, Inc., in active ingredient, conditions of use, route of administration, dosage form, strength and labeling; and that the two products are bioequivalent. The ANDA also provides a detailed description of the manufacturing and controls of the Andrx product.

This ANDA consists of 9 volumes. Two copies are provided — an archival copy (in blue folders) and a review copy separated into the bioequivalence review section (in orange folders) and the chemistry review section (in red folders). A detailed description of the organization of this ANDA is provided on introductory page (v) - Executive Summary, Organization of the ANDA.

In accordance with 21 CFR §314.94(d)(5), Andrx Pharmaceuticals, Inc. certifies that concurrent with this submission, a field copy has been forwarded to the Orlando District Office. This field copy is a true copy of the technical sections contained in the archival and review copies of the application.

Please direct any correspondence regarding this application to me at the address below. I may also be contacted by telephone at (954) 581-7500 or by fax at (954) 327-5389.

Sincerely,

David A. Gardner

David A. Gardner
V. P., Regulatory Affairs/QA/QC

RECEIVED
MAR 17 1998
GENERIC DRUGS

4001 S.W. 47TH AVENUE, SUITE 201, FORT LAUDERDALE, FLORIDA 33314 • 954-581-7500 • FAX: 954-587-1054

COVINGTON & BURLING

1201 PENNSYLVANIA AVENUE NW
WASHINGTON, DC 20004-2401
TEL 202.662.6000
FAX 202.662.6291
WWW.COV.COM

WASHINGTON
NEW YORK
LONDON
BRUSSELS
SAN FRANCISCO

BRUCE N. KUHLIK
TEL 202.662.5348
FAX 202.778.5348
BKUHLIK@COV.COM

Incorrect letter was posted on the internet. Being replaced. 1 /S/ 9/19/00 NEW CORRESP NC /S/

September 1, 2000

Office of Generic Drugs (HFD-600)
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: **ANDA 75-347 (Omeprazole Delayed-Release Capsules)**
Andrx Pharmaceuticals, Inc.

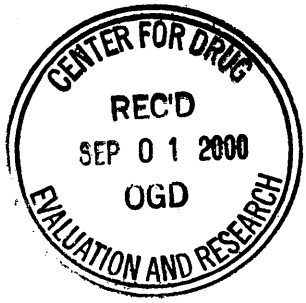
Dear Sirs:

This letter is submitted on behalf of AstraZeneca LP, which holds the approved new drug application for Prilosec, the reference listed drug referred to in the above-captioned abbreviated new drug application submitted by Andrx Pharmaceuticals, Inc.

In the tentative approval letter dated March 24, 2000, from FDA to Andrx concerning this ANDA (copy attached), FDA refers to patent litigation underway with respect to certain listed patents, including U.S. Patent No. 4,255,431 ("the '431 patent"). However, Andrx submitted a paragraph III certification for this patent, not a paragraph IV certification and, accordingly, Andrx has not been sued for infringement of this patent.

The purpose of this letter is to ensure that FDA correctly applies the statutory provisions relating to the effective date of the Andrx ANDA, with respect to the '431 patent. Because Andrx submitted a paragraph III certification with respect to this patent, the ANDA cannot be made effective before the expiration date of that patent, April 5, 2001, regardless of the disposition of litigation involving any of the other patents. In addition, omeprazole is the subject of a written request from FDA for pediatric information, and AstraZeneca anticipates qualifying for six months of pediatric exclusivity pursuant to section 505A of the Federal Food, Drug, and Cosmetic Act. This would mean that the ANDA could not be approved before October 5, 2001.

The dates described in the preceding paragraph relate only to the paragraph III certification made with respect to the '431 patent and thus represent the earliest date on which the ANDA would be eligible for approval based on that certification. If any other applicable period resulting from other patents, litigation, or exclusivity expires after that date, or if the



ANDA otherwise were not eligible for approval, then the ANDA could not be subject to a final approval until the expiration of the last applicable date. *See* 21 C.F.R. § 314.107(b)(4).

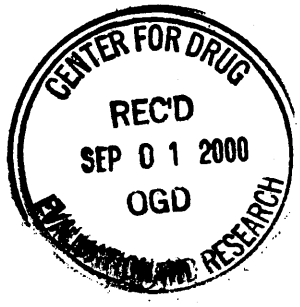
Sincerely yours,

Bruce N. Kuhlik

Counsel for AstraZeneca LP

cc: Andrx Pharmaceuticals, Inc.
Attention: Diane Servello

APPEARS THIS WAY
ON ORIGINAL



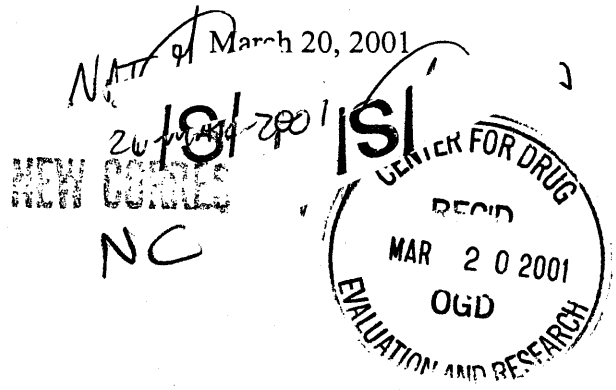
COVINGTON & BURLING

1201 PENNSYLVANIA AVENUE NW
WASHINGTON, DC 20004-2401
TEL 202.662.6000
FAX 202.662.6291
WWW.COV.COM

WASHINGTON, DC
NEW YORK
LONDON
BRUSSELS
SAN FRANCISCO

BRUCE N. KUHLIK
TEL 202.662.5348
FAX 202.778.5348
BKUHLIK@COV.COM

March 20, 2001



BY HAND

Office of Generic Drugs (HFD-600)
Food and Drug Administration
Metro Park North 2, Room 286
7500 Standish Place
Rockville, MD 20855

Re: **All ANDAs for Omeprazole Delayed-Release Capsules: ANDAs 75-268, 75-347, 75-410, 75-576, 75-757, 75-785, 75-791, 75-832, 75-876**

Dear Sirs:

This letter is submitted on behalf of AstraZeneca LP, which holds the approved new drug application for Prilosec® (NDA 19-810), the reference listed drug referred to in the above-captioned abbreviated new drug applications. Copies of this letter are being provided for each ANDA file.

The purpose of this letter is to ensure that the Office of Generic Drugs is aware of two recent developments affecting the timing of the approval of each of the omeprazole ANDAs.

First, AstraZeneca has recently listed four new patents with FDA in connection with the Prilosec NDA. On December 8, 2000, the CDER Central Document Room received information regarding U.S. Patents 6,150,380 and 6,147,103. On January 16, 2001, the CDER Central Document Room received information regarding U.S. Patent 6,166,213. On March 16, 2001, the CDER Central Document Room received information regarding U.S. Patent 6,191,148. AstraZeneca made these submissions within 30 days of the date of the issuance of the respective patents. Accordingly, each is deemed to have been listed on the date received by CDER (21 C.F.R. § 314.53(d)(4) and (5)). All four patents are now shown on FDA's web site (<http://www.fda.gov/cder/orange/docket.pdf>). Each ANDA must be amended to provide a certification as to each of these patents (21 C.F.R. § 314.94(a)(12)). As of today, only one of the ANDA applicants (Andrx, ANDA No. 75-347) has provided notice of a paragraph IV certification to the first three of these patents, and none has provided notice with respect to the fourth patent. At the earliest, none of the ANDAs can be made effective

until the expiration of 45 days following receipt of such notice (21 C.F.R. § 314.107(b)(3) and (f)). Of course, if litigation is instituted within the 45-day period, or if an ANDA submits a certification under paragraph III rather than paragraph IV, later dates would apply.

Second, AstraZeneca has filed pediatric study reports in response to a written request from FDA for pediatric information pursuant to section 505A of the Federal Food, Drug, and Cosmetic Act. Agency review of these reports is required no later than April 4, 2001, and the company expects to receive pediatric exclusivity as a result of that review. The award of pediatric exclusivity will add six months to all Prilosec patent and exclusivity periods for purposes of determining the dates on which the ANDAs can be approved. Of most immediate importance, for those applicants that certified under paragraph III to U.S. Patent No. 4,255,431, which expires on April 5, 2001, approval will be prohibited at least through October 5, 2001.

Each of the ANDA holders has made certifications to other patents listed for Prilosec and is the subject of infringement litigation brought within the applicable 45-day period. These certifications and lawsuits independently prohibit FDA approval of the ANDAs until specified dates. In addition, the 180-day exclusivity provision delays the approval of certain of the applications. The approval of any particular ANDA cannot be made effective until all of the applicable periods arising from the certifications, litigation, pediatric exclusivity, and 180-day exclusivity have expired (21 C.F.R. § 314.107(b)(4)).

Sincerely yours,

Bruce N. Kuhlik

Counsel for AstraZeneca LP

cc: ANDA 75-268 (Genpharm Inc.)
ANDA 75-347 (Andrx Pharmaceuticals, Inc.)
ANDA 75-410 (KUDCo)
ANDA 75-576 (Cheminor Drugs, Ltd.)
ANDA 75-757 (Lek Pharmaceutical & Chemical Co. d.d.)
ANDA 75-785 (Impax Laboratories, Inc.)
ANDA 75-791 (Eon Labs Manufacturing Inc.)
ANDA 75-832 (Zenith Goldline Pharmaceuticals, Inc.)
ANDA 75-876 (Mylan Pharmaceuticals Inc.)

Andrx
PHARMACEUTICALS, INC.

March 27, 2001

VIA FACSIMILE AND
OVERNIGHT DELIVERY

Mr. Gary Buehler
Acting Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855

Re: Unlawful Patent Listings for Prilosec®

Dear Mr. Buehler:

Andrx objects to the listing by Astra Merck, Inc. ("Astra") of four new patents, U.S. Patents No. 6,147,103, No. 6,150,380, No. 6,166,213 and No. 6,191,148, as covering the approved drug Prilosec® (omeprazole delayed-release capsules; NDA 19-810). Andrx believes that Astra is manipulating the patent listing provisions of the Hatch-Waxman amendments in an attempt to delay generic competition by Andrx's tentatively approved bioequivalent product. Consistent with the provisions of 21 U.S.C. § 355(c)(2), C.F.R. § 314.53 and FDA's longstanding limitation on patents that are listed in the Orange Book, Andrx requests that the agency require AstraZeneca to de-list the four newly-listed patents by next Monday, April 2, 2001.

In the first place, it would appear that at least the first three patents were not listed within the 30 days required by 21 C.F.R. § 314.53(d).

Second, the '103, '213, and '148 patents are each entitled "Omeprazole Process and Compositions Thereof" and the '380 patent also includes process claims, so they cannot be properly be listed under 21 CFR 314.53(b).

Third, to the extent any of the patents claim specific forms of omeprazole or compositions of omeprazole with specific levels of residual solvents or other chemicals, Andrx is unaware of any evidence

4955 ORANGE DRIVE, FORT LAUDERDALE, FLORIDA 33314 · 954 581-7500 · FAX: 954 587-1054

suggesting that Prilosec actually contains omeprazole in the form or composition claimed by the patents. The FDA is in a unique position to determine if Astra has amended its NDA to change the specification for the purity of the omeprazole that has been sold since at least 1990. If Astra has not notified the FDA of a change in its production process or products specification since the filing date of the four newly-listed patents and received all requisite approvals, the FDA has sufficient information in its own files to delist the newly listed patents.

Fourth, Andrx notes that the question of whether or not the patents are properly listed in the Orange Book is separate from the question of whether the listing can or should in any way delay FDA approval of Andrx's ANDA under 21 U.S.C. § 355(j)(5)(B)(iii). There is no statutory basis for such a delay, and in fact any such delay would be contrary to the clear wording of the statute.

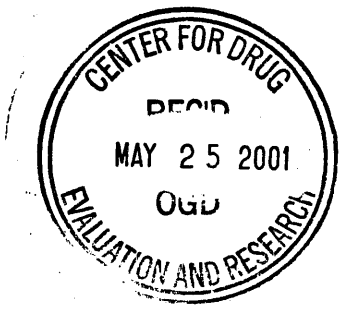
Andrx appreciates FDA's attention to this matter, but must reserve all its rights. Our outside counsel, King & Spalding, will contact your office to follow-up on this letter.

Sincerely,

Scott Lodin
Executive Vice President &General Counsel

cc: Drug Information Services Branch (HFD-84)
Mr. Donald B. Hare, Office of Generic Drugs (HFD-604)
Kim E. Dettelbach, Esq., Office of the Chief Counsel (GCF-1)

Eugene M. Pfeifer, Esq.
Christina M. Markus, Esq.
King & Spalding



Andrx
PHARMACEUTICALS, INC.

May 29, 2001

Gary Buehler,
Acting-Director, Office of Generic Drugs, HFD-600
CDER, Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NEW CORRESP

PATENT AMENDMENT
ANDA 75-347 – Omeprazole Delayed-release Capsules, 10 mg, 20 mg and 40 mg

Dear Mr. Buehler:

Andrx Pharmaceuticals, Inc. is amending the above referenced application to provide documentation of notification and receipt of notice, as follows:

Documentation of Notification /Receipt of Notices:

In accordance with 21 CFR 314.95(b), Andrx certifies that:

i. the required notices of certification of noninfringement of patents 6,147,103; 6,166,213 and 6,150,380 were provided on March 16, 2001 by Federal Express and U.S. Postal Service Express Mail, return receipt requested to each person identified under §314.95(b) (i.e.Astra Zeneca, LP; Merck & Co., Inc.; and Astra Aktiebolag). The Federal Express tracking documents indicate that the notices were received on March 19, 2001. The U.S. Postal tracking documents indicate that the notice to Merck was received on March 19, 2001 and the notice to Astra Aktiebolag was received on March 21, 2001. We have not received the return receipt from Astra Zeneca, LP.

ii. the required notices of certification of noninfringement of patent 6,191,148 were provided on March 22, 2001 by Federal Express and U.S. Postal Service Express Mail, return receipt requested to each person identified under §314.95(b) (i.e.Astra Zeneca, LP; Merck & Co., Inc.). The Federal Express tracking documents indicate the notices were received on March 27, 2001. The U.S. Postal tracking documents indicate that Astra Zeneca, LP received the notice on March 27, 2001 and Merck & Co., Inc. received the notice on March 26, 2001.

iii. the notices met the content requirements under §314.95(c).

Please see the attached summary table referencing the above information. Copies of the return receipt postcards and the delivery tracking reports are enclosed.

Based on the latest date (March 27, 2001) documented on the return receipts, the 45-day period, provided for in section 505(J)(4)(B)(iii) of the act, ended on May 11, 2001. As of today's date, no litigation has been filed by the patent holder or the NDA holder. Should you have any questions regarding this amendment, please do not hesitate to contact Janet Vaughn at (954) 585-1665 *(Tel.)* or (954) 587-1054 *(Fax)*.

Sincerely,

Diane Servello
Director, Regulatory Affairs

Enclosure(s)

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
MAY 31 2001
OGD

4955 ORANGE DRIVE, FORT LAUDERDALE, FLORIDA 33314 • 954 581-7500 • FAX: 954 587-1054